Received: 12 September 2020 | Revised: 4 January 2021 | Accepted: 12 January 2021

DOI: 10.1002/ptr.7039

REVIEW

WILEY

Medicinal plants: Treasure for antiviral drug discovery

Sofi Imtiyaz Ali[1] | Wajid Mohammad Sheikh[1] | Muzafar Ahmad Rather[1] | Venugopalan Venkatesalu[2] | Showkeen Muzamil Bashir[1] | Showkat Ul Nabi[3]

[1]Biochemistry & Molecular Biology Lab, Division of veterinary Biochemistry, Faculty of Veterinary Sciences and Animal Husbandry, SKUAST-K, Srinagar, India

[2]Department of Botany, Annamalai University, Annamalainagar, India

[3]Large Animal Diagnostic Laboratory, Department of Clinical Veterinary Medicine, Ethics & Jurisprudence, Faculty of Veterinary Sciences and Animal Husbandry, SKUAST-K, Srinagar, India

Correspondence
Showkeen Muzamil Bashir, Biochemistry & Molecular Biology Lab, Division of Veterinary Biochemistry, F.V.Sc. & A.H, Shuhama, Alusteng, Srinagar-190006, Jammu & Kashmir, India.
Email: showkeen@skuastkashmir.ac.in

Showkat Ul Nabi, Large Animal Diagnostic Laboratory, Department of Clinical Veterinary Medicine, Ethics & Jurisprudence, F.V.Sc. & A. H, SKUASTt-K, Shuhama, Alusteng, Srinagar-190006, Jammu & Kashmir, India.
Email: showkatnabi@gmail.com

The pandemic of viral diseases like novel coronavirus (2019-nCoV) prompted the scientific world to examine antiviral bioactive compounds rather than nucleic acid analogous, protease inhibitors, or other toxic synthetic molecules. The emerging viral infections significantly associated with 2019-nCoV have challenged humanity's survival. Further, there is a constant emergence of new resistant viral strains that demand novel antiviral agents with fewer side effects and cell toxicity. Despite significant progress made in immunization and regenerative medicine, numerous viruses still lack prophylactic vaccines and specific antiviral treatments that are so often influenced by the generation of viral escape mutants. Of importance, medicinal herbs offer a wide variety of therapeutic antiviral chemotypes that can inhibit viral replication by preventing viral adsorption, adhering to cell receptors, inhibiting virus penetration in the host cell, and competing for pathways of activation of intracellular signals. The present review will comprehensively summarize the promising antiviral activities of medicinal plants and their bioactive molecules. Furthermore, it will elucidate their mechanism of action and possible implications in the treatment/prevention of viral diseases even when their mechanism of action is not fully understood, which could serve as the base for the future development of novel or complementary antiviral treatments.

KEYWORDS
2019-nCoV, antiviral chemotypes, medicinal plants, phytomolecules, viral infections

1 | INTRODUCTION

Among all the numerous outbreaks of infectious diseases confronted by humankind, it's indeed the viral infections that are undoubtedly the biggest pandemic threat in the recent era. The replication patterns and viral modes of transmission are the main determinants underpinning this assault. A wide-spectrum antiviral agent's inadequacy plays a pivotal role (Center for Health Security, 2019). Viruses need to use host cell machines for several functions. Therefore, their obligatory parasitic nature and antiviral approaches must be applied directly to a virus to minimize interference with the host cell functions (Adalja & Inglesby, 2019).

Further, the virus acts as barriers to broad-spectrum antiviral agents, including distinctions among RNA and DNA viruses, completely distinct virally encoded proteins, single or double genomic structure, cycles of cytoplasmic or nuclear replication, and degree of dependence on host proteins (Schoeman & Fielding, 2019). The global antiviral drug armamentarium is expanding exponentially and is now covering many viral families. Nonetheless, very few known antiviral agents have activity spectrums that even marginally match up to the penicillin or sulfa range, the very first antibacterial agents identified.

The Earth's planet constitutes approximately 1,031 viruses, and their pervasiveness has colonized the marine ecosystem, where about 5,000 viral genomes seem to be prevalent in every 200 L of water (Breitbart & Rohwer, 2005). Also, viruses continue moving between the environments. They are available worldwide, for example, in deep Ocean, polar ices, alkaline, hot, and salt waters, and are about 2,000 m deep in the terrestrial ecosystem. There have been nearly 20 families

of viruses that certainly infect humans (Harvey, Champe, Fisher, & Strohl, 2006), and many of them also trigger diseases in animals (Mahzounieh, Moghtadaei, & Zahraei Salehi, 2006). Virus particles contact the living system, and if they inundate the human immune response, then preventing their expansion in the body would be almost unfeasible. For the sake of their frequent replication, they control the host biochemical pathway/metabolic processes and make their treatment almost tricky. However, it is now well comprehended that viruses are specific in their replication mode that could be effectively approached (Syed, Amako, & Siddiqui, 2010). For instance, the proteolytic enzyme enhances viral maturation by distinguishing the viral polyprotein predecessor, whose obstruction would prevent its growth (Wapling, Srivastava, Shehu-Xhilaga, & Tachedjian, 2007). The epidemic outbreaks caused by emerging and re-emerging viruses represent a critical threat to public health, mainly when preventive vaccines and antiviral therapies are unavailable. Several hard-to-cure diseases and complex syndromes, including Alzheimer's disease, type 1 diabetes, and hepatocellular carcinoma (HCC), have also been associated with viral infection (M. J. Ball, Lukiw, Kammerman, & Hill, 2013; Hober et al., 2012; Morgan et al., 2013). However, many viruses remain without adequate immunization and, only a few antiviral drugs are licensed for clinical practice. The situation is further exacerbated by drug-resistant mutants' especially when using viral enzyme-specific inhibitors, which significantly hampers drug efficacy (Geretti, Armenia, & Ceccherini, 2012; Locarnini & Yuen, 2010). Hence, there is an urgent need to discover novel antivirals that are highly productive and cost-effective for managing and controlling viral infections when vaccines and standard therapies lack.

New viral infections needed quite advanced drug molecules; however, the process of establishing such approaches toward this moment seems to have been sluggish and filled with impediments (Desselberg, 2000). Antiviral chemotherapy has proceeded at a snail-like pace, unlike antibiotics that had attained a specific treatment level in three decades. Nevertheless, it ended up taking nearly 60 years for antiviral development to achieve its current prevalence position. The evolution of diagnosis for Hepatitis C is a prime illustration of how complicated the antiviral effect can be. However, cumulative and aimed antiviral therapy has proven to be an excellent strategy for treating viral infectious disease.

Viruses are amongst the substantial causes of mortality and morbidity globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; WHO, 2015). Antiviral drugs and vaccines are being used to control human viral infections (De Clercq & Li, 2016). Eventually, the main focus was on "one drug, one virus" dogma, which depends solely on targeting virus-specific factors. A counterstatement to this is "one drug multiple viruses" (BSAAs), as viruses utilize similar pathways and host factors to replicate within a cell (Bekerman & Einav, 2015; Bosl et al., 2019; de Clercq & Montgomery, 1983; De bing, Neyts, & Delang, 2015; Ianevski, Andersen, Merits, Bjoras, & Kainov, 2019; Rada & Dragun, 1977; Sidwell et al., 1972). Though the concept of BSAAs was about 50 years ago, due to the recent outbreaks of a novel coronavirus (2019-nCoV) and several other viral infections, the field has acquired new urgency for the discovery of novel host-directed agents and the expansion of a drug repositioning methodology (Paraskevis et al., 2020).

Drug repurposing, also known as repositioning, redirecting, reprofiling, is a strategic approach for accumulating additional benefits from an approved drug by approaching a disease apart from that it was initially envisioned (Nishimura & Hara, 2018; Pushpakom et al., 2019). It has distinct advantages over new drug discovery since chemical synthesis, manufacturing processes, reliable safety, and pharmacokinetic properties are accessible in pre-clinical and early clinical development phases. Consequently, the repositioning of launched or perhaps failed viral drugs offer incredible translational opportunities, such as a substantially higher probability of commercial success in comparison to the implementation of novel virus-specific medicines and vaccines and a substantially decreased cost and timeframe for clinical accessibility (Ianevski et al., 2019; Pizzorno, Padey, Terrier, & Rosa-Calatrava, 2019; Zheng, Sun, & Simeonov, 2018).

Antivirals are antimicrobial compounds derived from living organisms or generated by chemical synthesis, mostly hindering viral replication. Antivirals tamper with one or more phases of the viral life cycle, which include: cell attachment, cell penetration, viral uncoating, copy of the viral genome (DNA/RNA), maturation, and reveal of viral progeny and, are an essential tool to facilitate vaccine action (Veiga-Crespo, Viñas, & Villa, 2015). The synthesized antiviral drugs such as moroxydine, ganciclovir, valganciclovir, and valaciclovir were used to inhibit virus replication through various mechanisms (Biron, 2006). However, due to their low efficacy, cytotoxicity, and the development of viral resistance, difficulties in treating drugs arise. A further antiviral therapy, vaccination, may be used but is still under advancement because it often provides inadequate virus protection, and its validity needs further investigation (Subbarao & Joseph, 2007). Thus, more scientific research is required in the treatment of antiviral synthetic drugs and vaccines.

Nature has provided yet another credible source of antiviral agents, and almost 40% of the drugs available at the moment are directly or indirectly plant derivatives. A range of ethnobotanical studies focused on identifying possible therapeutic plants for even more effective management of healthcare issues, demonstrating the significance of medicinal plants in the healthcare deliveray system (Ansari & Inamdar, 2010; Appidi, Grierson, & Afolayan, 2008; Heneidy & Bidak, 2004; Ky et al., 2009; Makambila-Koubemba, Mbatchi, Ardid, Gelot, & Henrion, 2011; Shinwari & Khan, 2000). Herbal remedies and extracted natural products often provide a significant source of novel antiviral developing drugs. Antiviral medications' characterization from such natural sources sheds light on where they interrelate with the viral replication cycle, like viral entry, replication, assembly, and release, and the targeting of precise virus–host interactions. Here, we enumerate the antiviral activities of a range of natural products and herbal medicines against specific critical viral pathogens. This study aims to assess previously published antiviral plants and spot possible action mechanisms and substances accountable for their antiviral activity. A deeper understanding of the mode of action and evaluating the concerned compounds will provide a unique insight into the concept of new antiviral drugs for even more effective viral co-operation.

2 | METHODOLOGY

An extensive review of the literature was carried out on antiviral medicinal plants and their associated bioactive compounds between 2019 and 2020 via electronic search Pubmed, Scopus, Web of Science, Science Direct, J-Gate, Google Scholar, and a library search for articles published in peer-reviewed journals. The unpublished materials have been excluded from this review. The review process was further continued by the refining of the search results using the keywords namely viral medicinal plants, antiviral bioactive compounds, emerging viral infections, novel coronavirus, coxsackievirus (CV), dengue virus (DENV), enterovirus 71, human herpes viruses, hepatitis virus, human immunodeficiency virus, influenza virus, measles virus (MV), respiratory syncytial virus (RSV), and rotavirus. The literature cited in the review dated from 1950 to 2020 and limited to the English language. The final data collected through the authors' discussions were then compiled, evaluated, compared, and drawn accordingly.

3 | BASIC VIRAL STRUCTURE AND ITS PATHOBIOLOGY

Viruses are organic artifacts that are metabolically inactive outside the host and after accessing the host cell becomes activated (Dupre & O'Malley, 2009). They are comprised primarily of proteins and nucleic acid; the proteins contribute to their unique shape by forming a capsid (Andersson, 2010). Therefore, viruses are of different forms, like superficial, helical, icosahedral, or complex, and perhaps some viruses are accompanied by a lipid bilayer extrapolated from a host membrane called an envelope (Geng et al., 2007). Besides, capsid proteins associated with nucleic acids form nucleocapsids. Proteins related to viral nucleic acids are called nucleoproteins. Virus nucleic acid is either DNA or RNA and has been the elementary source of knowledge required to monitor its metabolic functions. This DNA and RNA are categorized based on the number of strands into single or double-stranded DNA/RNA (Firth et al., 2010; Pichlmair et al., 2006). The sense of strand can further differentiate single-stranded RNA viruses as some RNA viruses have a positive-sense RNA (+ve ssRNA), and some viruses have a negative-sense RNA (−ve ssRNA) (Gorbalenya, Enjuanes, Ziebuhr, & Snijder, 2006). Nucleic acid form (DNA/RNA) is indeed a vital point of differentiation since all viruses did not constitute the same nucleic acid pattern (Gao & Hu, 2007).

The multiplication of all viruses results from several sequential processes: adhesion of the virus to the cell surface, virus adsorption and entry into the cell, replication of viral nucleic acids, and expression of viral proteins, and release of virus particles from the cell. For example, the virus entrance process is often carried out by cell surface proteins; Hepatitis C virus (HCV) entry involves claudin-1, occludin, and tetraspanins as the primary receptor proteins (Burlone & Budkowska, 2009). The latter's accession is influenced by other lipoproteins and the enzyme lipoprotein lipase. Moreover, infection with the influenza virus is modulated by a protease enzyme that triggers the viral surface protein hemagglutinin (Zambon, 2001). The protease enzyme is pertinent for illustrating viral proteins; it categorizes proteins into groups based on everyone's structural and non-structural features (Appel, Schaller, Penin, & Bartenschlager, 2006). But RNA viruses require two powerful enzymes to sustain; reverse transcriptase and integrase, former transcribed viral RNA to DNA at the moment of replication (Briones, Dobard, & Chow, 2010; Sluis-Cremer & Tachedjian, 2008). In contrast, the second enzyme integrates viral DNA into the host genome and is required for the effective uncoating of virus-core proteins. As a result, the virus needs enzymatic and non-enzymatic proteins to stop its replication and infection.

4 | ANTIVIRAL MOLECULES OF PLANT ORIGIN

Conventional medicine is indeed a worthwhile line of study for analyzing, extracting, and developing medicinal benefits. Conversely, a relatively small proportion of bioactive compounds were studied systematically for their therapeutic uses. Natural products include an unusual approach to exploring antiviral agents with remarkable pharmacological properties (Cragg & Newman, 2013; Atanasov et al., 2015). Herbal therapists have been using traditional plants since prehistoric days to cure diseases in humans and animals, particularly in the Asia-Pacific region. People continue to rely on medicinal herbs and their products for their wellness and primary medical care throughout the globe (Ekor, 2014). About 2,500 natural plant species are listed globally to diagnose many diseases and illnesses (Kapoor, Sharma, & Kanwar, 2017).

Collecting traditional data from local or indigenous communities or even using important ethnopharmacology plant(s) to extract bioactive molecules/phytochemicals is a very demanding approach for diagnosing different ailments (Altemimi, Lakhssassi, Baharlouei, Watson, & Lightfoot, 2017). Numerous aspects, including the various solvents (polar, non-polar) used during the extraction of bioactive constituents and the selection of plant parts/tissue for their extraction from plants, commonly play a crucial role (Ben-Shabat, Yarmolinsky, Porat, & Dahan, 2020). A holistic approach for isolating and characterizing bioactive molecules and virus replication inhibitory experiments in animal cell systems is required when such bioactive molecules could be used to cure a viral infection (Kapoor et al., 2017). The eternal objective of establishing high throughput screening assays is just the way to recognize bioactive molecules/phytochemicals from large chemical libraries quickly and accurately. In vivo experiments and consequent clinical studies are necessary to identify the antiviral activity and severe complications like reactogenicity or toxicity of purified bioactive molecules.

4.1 | Coronavirus and medicinal plants

Coronavirus (CoV) is a single-stranded, positive-sense envelope (ss-RNA) virus (Family: coronaviridae). The CoV family comprises many

species responsible for causing respiratory and gastrointestinal infections in mammals and birds. It mostly leads to cold or flu in human beings, yet complications could emerge, such as pneumonia and severe acute respiratory syndrome (SARS) (Van-der Hoek, 2007). The documented CoV (HCoV) comprises HCoV-229E, -OC43, -NL63, -HKU1, and the universally recognized severe acute respiratory coronavirus syndrome (SARS-CoV), which triggered a high mortality threat to the world in 2003 (Geller, Varbanov, & Duval, 2012). In 2012, the World Health Organization (WHO) reported a sixth highly lethal form of HCoV infection known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (WHO, 2013).

The severe acute coronavirus 2 respiratory syndromes (SARS-CoV-2) was first reported in December 2019 in Wuhan, Hubei, China, and declared by the World Health Organization (WHO) as a pandemic on March 11, 2020 (WHO, 2020). The tentative name 2019-nCoV was given by the World Health Organization, later by the International Committee on Taxonomy of Viruses renamed it as SARS-CoV-2 (Coronavirus disease 2019). The Wuhan strain was recognized as a new strain of Group 2B Betacorona virus with nearly 70% genetic ancestry to SARS-CoV (Hu, Azhar, Madani, & Ntoumi, 2020). The virus seems to have a 96% resemblance to the coronavirus bat, and therefore it is generally believed to emanate from bats. There seem to be no precise medications or treatment options for COVID-19; however, numerous clinical trials assessing possible treatments are continuing during this period (WHO, 2020).

Coronaviruses are large pleomorphic spherical particles with a bulbous surface projection. The diameter of the virus particles is approximately 120 nm (Fehr, Perlman, Maier, Bickerton, & Britton, 2015). The virus membrane in electron micrographs did appear as a unique pair of thick electron shells. The viral envelope consists of a lipid bilayer under which the membrane, envelope, and spike structural proteins are situated. A beta coronavirus subgroup A have a shortened spike-like surface protein called hemagglutinin esterase (HE) (Neuman, Kiss, Kunding, Bhella, & Baksh, 2011).

Moreover, nucleocapsid develops copies of the nucleocapsid protein attached to the positive-sense single-stranded RNA genome (Fehr et al., 2015). The genome size for coronaviruses ranges from 27 to 34 kilobases, the largest among documented RNA viruses. The lipid bilayer envelope, membrane protein, and nucleocapsid safeguard the virus outside the host cell (Neuman et al., 2011). There is only one amino acid variation in specific genome sequences among viruses discovered in pangolins and viruses found in humans.

Interestingly, about 92% of the genetic material accessed between pangolin coronavirus and SARS-CoV-2 has been identified as a complete genome comparison to date that is grossly inadequate to demonstrate that pangolins are intermediate hosts (Cyranoski, 2020). The virus does have a 96% resemblance to the coronavirus bat, and therefore it is generally believed that it emanates from bats (Cohen, 2020). The name coronavirus is derived from the Latin word corona, which means "crown" or "halo," which pertains to the characteristic appearance of the crown or solar corona around the virions (virus particles) under two-dimensional electron microscopy, due to the surface covering of the club-shaped protein spikes.

There have been no specific treatments for CoV infection, and preventive vaccines are still under examination. It illustrates the need to implement new antivirals for prophylaxis and treatment of CoV infection. The complete list of the potent plant extracts and their bioactive compounds that inhibit coronavirus are depicted in Table 1. Ginsenoside Rb1 (Gynosaponin C), one of the bioactive ginsenosides extrapolated from *Panax ginseng*, displayed antiviral activity (Wu et al., 2004). Tetra-O-galloyl-beta-D-glucose, luteolin, and tetra-O-galloyl-beta-D-glucose, blocked the SARS-CoV host cell entry (Yi et al., 2004). Chinese herbs have long been known for their antiviral effects and therefore examined for SARS-CoV's potential role. Of the 200 herbal extracts analyzed, *Lycoris radiata*, *Artemisia annua*, *Pyrrosia lingua*, and *Lindera aggregata* seemed to have an anti-SARS-CoV impact with a 50% effective aa(EC_{50}) of 2.4–88.2 μg/ml (Li et al., 2005a). Additionally, tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3′-digallate, three black tea phenolics, collectively, exhibited inhibitory effects SARS-CoV 3CLpro with IC_{50} values of 3, 7, and 9, 5 μM, respectively (Chen et al., 2005). On the other hand, phenolic compounds from *Isatis indigotica* showed an inhibitory effect against SARS-CoV 3CLpro with IC_{50} values of 217, 752, 8.3, 365, and 1,210 μM, respectively for sinigrine, indigo, aloe emodin, hesperetine, and β-sitosterol (Lin et al., 2005).

Saikosaponins (A, B2, C, and D), naturally occurring triterpene glycosides obtained from *Bupleurum* spp., *Heteromorpha* spp., and *Scrophularia scorodonia*, exhibited antiviral activity against HCoV-22E9. Saikosaponin A, B2, C, and D have efficacy toward human CoV-229E, with EC_{50} values of 8.6, 1.7, 19.9, and 13.2 μM, respectively; saikosaponin B2 subdued viral attachment and penetration stages (Cheng et al., 2006a). These natural compounds effectively avoid the initial stage of HCoV-22E9 infection, like viral attachment and penetration, following co-challenge with the virus. In contrast, *Rheum officinale*, *Polygonum multiflorum*, and emodin have been investigated and proven to suppress SARS-CoV (S) protein and ACE2 interaction with IC_{50} valuesHo et al., 2007). Among 221 phytochemicals studied against SARS-CoV, 10 diterpenes, two sesquiterpenes, two triterpenes, and five lignans curcumin exhibited inhibitory effects at 3–10 μM concentration (Wen et al., 2007).

Interestingly, psoralidin showed a strong protease inhibitor influence on SARS-CoV with an IC_{50} value of 4.2 μM. Simultaneously, emodin, rhein, and chrysin hindered SARS-CoV (S) and ACE2 protein–protein interaction at 0–400 μM (T. Y. Ho et al., 2007; Kim et al., 2007). Conversely, ferruginol, 8β-hydroxyabieta-9(11),13-dien-12-one, 3β,12-diacetoxyabieta-6,8,11,13-tetraene, betulonic acid, betulinic acid, hinokinin, savinine, and curcumin inhibits replication of SARS-CoV at 0–80 μM (Wen et al., 2007). Other natural anti-CoV molecules include water extract from *Houttuynia cordata*, which displayed antiviral mechanisms against SARS-CoV, such as viral 3CL protease inhibition and viral RNA-dependent polymerase activity blockage (Lau et al., 2008). In the same way, *Toona sinensis* aqueous leaf extract inhibited SARS-CoV replication with EC_{50} values ranging from 30 to 40 μg/ml and SI values ranging from 12 to 17 (Chen et al., 2008). Procyanidin A2, procyanidin B1, and cinnamon tannin B1, extracted from *Cinnamomi cortex*, also hindered SARS-CoV infection at 0–500 μM (Zhuang et al., 2009).

TABLE 1 List of the potent extracts bioactive compounds that inhibit Coronavirus

Natural product(s) evaluated	Test system	Test dose	Proposed mechanism	References
Lycoris radiate	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Artemisia annua	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Pyrrosia lingua	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Lindera aggregata	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Isatis indigotica	SARS-CoV	1–500 μg/ml	3CL protease inhibition	Li et al., 2005a
Extract (*Rheum officinale* Baill., *Polygonum multiflorum* Thunb.)	SARS-CoV spike (S) Protein	0–100 μg/ml	Inhibits the interaction of SARS-CoV S protein and ACE2	Ho, Wu, Chen, Li, & Hsiang, 2007
Houttuynia cordata Aq. Extract	SARS-CoV	0–400 μg/ml	3CL protease and viral polymerase inhibition	Lau et al., 2008
Herbal extracts (*Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, *Taxillus chinensis*, *Cibotium barometz*)	SARS-CoV	25–200 μg/ml	3CL protease inhibition	Wen et al., 2011
Anthemis hyalina, *Nigella sativa*, and *Citrus sinensis* Extracts	SARS-CoV	1/50 and 1/100 dilution of ethanolic (100 g/200 ml)	Increased IL-8 level. Significantly changed the expression of *TRPA1*, *TRPC4*, *TRPM6*, *TRPM7*, *TRPM8*, and *TRPV4*genes	Ulasli et al., 2014

Natural product(s) evaluated	Test system	Dose/concentration	Proposed mechanism(s)	References
Lycoris radiate	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Artemisia annua	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Pyrrosia lingua	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Lindera aggregate	SARS-CoV	10^{-1}–10^{-4} mg/ml	Undefined	Li et al., 2005a
Isatis indigotica	SARS-CoV	1–500 μg/ml	3CL protease inhibition	Li et al., 2005a
Extract (*Rheum officinale* Baill., *Polygonum multiflorum* Thunb.)	SARS-CoV spike (S) protein	0–100 μg/ml	Inhibits the interaction of SARS-CoV S protein and ACE2.	Ho et al., 2007
Houttuynia cordata Aq. Extract	SARS-CoV	0–400 μg/ml	3CL protease and viral polymeraseinhibition	Lau et al., 2008
Herbal extracts (*Gentiana scabra*, *Dioscorea batatas*,*Cassia tora*, *Taxillus chinensis*, *Cibotium barometz*)	SARS-CoV	25–200 μg/ml	3CL protease inhibition	Wen et al., 2011
Anthemis hyalina, *Nigella sativa*, and *Citrus sinensis* Extracts	SARS-CoV	1/50 and 1/100 dilution of ethanolic (100 g/200 ml)	Increased IL-8 level. Significantly changed The expression of *TRPA1*, *TRPC4*, *TRPM6*, *TRPM7*, *TRPM8*, and *TRPV4*genes	Ulasli et al., 2014
Aloe emodin, Beta-sitosterol, Hesperetin, Indigo and Sinigrin (*Isatis indigotica*)	SARS-CoV	1–100 μg/ml	3CL protease inhibition	Lin et al., 2005
Amentoflavone (*Torreya nucifera*)	SARS-CoV	1–1,000 μM	3CL protease inhibition	Ryu et al., 2010
Apigenin (*Torreya nucifera*)	SARS-CoV	1–1,000 μM	3CL protease inhibition	Ryu et al., 2010
Bavachinin (*Psoralea corylifolia*)	SARS-CoV	1–150 μM	Inhibitors of papain-like protease (PLpro)	Kim et al., 2014a
Rosmariquinone and Tanshinone I (*Salvia miltiorrhiza*)	SARS-CoV	1–1,000 μM	Inhibition of SARS-CoV viral infection and replication	Park et al., 2012

(Continues)

TABLE 1 (Continued)

Natural product(s) evaluated	Test system	Dose/concentration	Proposed mechanism(s)	References
Cinanserin (1 dpi) and Cinanserin (2 dpi) (*Houttuynia cordata*)	Murine CoV	15.63–500 μg/ml	Undefined.	Chiow et al., 2016
Cinnamtannin B, Procyanidin A2 and B1(*Cinnamomi cortex*)	SARS-CoV	0–500 μM	Inhibition of pseudovirus infection	Zhuang et al., 2009
Corylifol and Psoralidi (*Psoralea corylifolia*)	SARS-CoV	1–150 μM	Inhibitors of papain-like protease (PLpro)	Kim et al., 2014a
Dieckol, 7-Phloroeckol, Phlorofucofuroeckoln and Eckol (*Ecklonia cava*)	Porcine epidemic diarrhea CoV	1–200 μM	Inhibition of viral replication/Blockage of the binding of virus to ce	Kwon et al., 2013
Diplacone, Tomentin A, B, C, D, E (*Paulownia tomentosa*)	SARS-CoV	0–100 μM	Inhibition of papain-like protease	Cho et al., 2013
Broussochalcone A and B, 4-Hydroxyisolonchocarpin, Papyriflavonol A, Kazinol A, B, F, J and 3-(3-methylbut-2-enyl)-3,4,7-trihydroxyflavan (*Broussonetia papyrifera*)	3-chymotrypsin-like and papain-like coronavirus cysteine proteases	0–200 μM	Protease inhibition	Park et al., 2017
Isobavachalcone (*Psoralea corylifolia*)	SARS-CoV	1–150 μM	Inhibitors of papain-like protease (PLpro)	Kim et al., 2014
3-Isotheaflavin-3-gallate and tannic acid (black tea)	SARS-CoV	4–20 μM	Inhibition of 3C-like protease (3CLPro)	Chen et al., 2005
Luteolin and Quercetin (*Torreya nucifera*)	SARS-CoV	1–1,000 μM	3CL protease inhibition	Ryu et al., 2010
Lycorine (*Lycoris radiata*)	SARS-CoV	10^{-1}–10^{-4}	Undefined	Li et al., 2005a
Quercetin and Rutin (*Houttuynia cordata*)	Murine CoV	500–15.63 μg/ml	Undefined	Chiow et al., 2016
Glycoside juglanin (Quercus ilex)	SARS-CoV	10–40 μM	Blocks the 3a channel	Schwarz et al., 2014
4′-O-methylbavachalcone and Neobavaisoflavone (*Psoralea corylifolia*)	SARS-CoV	1–150 μM	Inhibitors of papain-like protease (PLpro)	Kim et al., 2014a
Mimulone, 3′-O-methyldiplacol, 4′-O-methyldiplacol, 3′-O-methyldiplacone, 4′-O-methyldiplacone (*Paulownia Tomentosa*)	SARS-CoV	0–100 μM	Inhibition of papain-like protease	Cho et al., 2013
7-Methoxycryptopleurine and Tylophorine (*Tylophora indica*)	CoV-infected swine testicular cells	-	Inhibition of viral replication	Yang et al., 2010
Saikosaponins A, B_2, C, D	HCoV-22E9	5–25 μM/L	Saikosaponin B_2 inhibits viral attachment and penetration stages	Cheng et al., 2006
Tylophorin	CoV	0–100 μM	Targeting viral RNA replication and Cellular JAK2 mediated dominant NF-κB activation	Yang et al., 2017

TABLE 1 (Continued)

Natural product(s) evaluated	Test system	Dose/concentration	Proposed mechanism(s)	References
Scutellarein	SARS-CoV	0.01–10 μM	3CL protease inhibition	Yu et al., 2012
Savinin	SARS-CoV	8–80 μM	Inhibition of 3CL protease	Wen et al., 2007
Silvestrol	HCoV-229E	0.6–2 μM	Inhibition of cap-dependent viral mRNA translation	Muller et al., 2018
Tetrandrine	HCoV-OC43	2–20 μM	Undefined	Kim et al., 2019
Phenazopyridine	HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59	0–5 μM	Undefined	Shen et al., 2019
Mycophenolatemofeti	HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59	0–5 μM	Immune suppression	Shen et al., 2019
Lycorine	HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59	0–5 μM	Inhibited cell division	Shen et al., 2019
Emetine	HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59	0–5 μM	Inhibited RNA, DNA and protein synthesis	Shen et al., 2019
Berbamine	HCoV-NL63	0–20 μM	Undefined	Shen et al., 2019
Fangchinoline	HCoV-OC43-infected MRC-5 human lung cells	2–20 μM	Undefined	Kim et al., 2019

Flavones and biflavones isolated from *Torreya nucifera* exude cytotoxic effect on SARS-CoV 3CLpro (Ryu et al., 2010), and Tylophorin and 7-methoxycryptopleurine isolated from *Tylophora indica* inhibit both N and S protein function and viral replication of enteropathogenic coronavirus transmissible gastroenteritis virus (Yang et al., 2010). Such molecules showed incredible antiviral activity with IC_{50} values of 0.018 and <0.005 μM, respectively. Tylophorine and 7-methoxycryptopleurine separated from *T. indica* have been shown to impede viral replication in coV-infected swine testicular cells (Yang et al., 2010). Six plant extracts (*Gentiana scabra*, *Dioscorea batatatas*, *Cassia tora*, *Taxillus chinensis*, *Cibotium barometz*) asserted inhibitory effect against SARS-CoV 3CLpro with IC_{50} values of 39 and 44 μg/ml, respectively (Wen et al., 2011). Besides, diterpenoid, 8b-hydroxyabieta-9 (11), 13-dien-12-one, and lignin, savinin were reported to prevent SARS-CoV 3CLpro activity with a SI >667. In comparison, betulinic acid and savinin were found competitive inhibitors of SARS-CoV 3CLpro with Ki values of 8.2 and 9.1 μM, respectively. Tanshinones (e.g., tanshinone I, rosmariquinone) derived from *Salvia miltiorrhiza* also hindered infection and replication of SARS-CoV 3CLpro and PLpro at 1–1000 μM (Park et al., 2012). Further, myricetine and scutellarein exert an inhibitory effect of 0.01–10 μM for SARS-CoV 3CLpro (Yu et al., 2012). Likewise, (–) catechin gallate and (–)-gallocatechin gallate at 0.001–1 μg/ml prevented SARS-CoV nanoparticle RNA oligonucleotide (Roh, 2012).

Further, Eckol, 7-phloroeckol, phlorofucofuroeckoln, and dieckol segregated from *Ecklonia cava* obstructed virus adhesion to porcine epidemic cells at 1–200 μM with IC_{50} values of 22.5, 18.6, 12.2, and 14.6 μM, respectively (Kwon et al., 2013). Similarly, tomentine A, B, C, D, and E, 3′-O-methyldiplacol, 4′-O-methyldiplacol, 3′-O-methyldiplacone, 4′-O-methyldiplacone, mimulone, diplacone, and 6-geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxyflavanone isolated from *Paulownia tomentosa* have been reported to suppress SARS-CoV PLpro at 0–100 μM (Cho et al., 2013). *Anthemis hyalina*, *Nigella sativa*, and *Citrus sinensis* extracts significantly reduced viral infection after HeLa-CEACAM1a (HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a) has been afflicted with MHV-A59 (Mous Hepatitis Virus – A59) CoV, with *A. hyalin* being the most effective of the three plants assessed. Even though TRP gene expression was reduced upon diagnosis with these extracts, a rise in calcium ion level made it unconvincing to equate this impact with reduced viral replication (Ulasli et al., 2014). In another report, bavachinin, neobavaisoflavone, isobavachalcone, 4′-O-methylbavachalcone, psoralidin, and corylifol isolated from *Psoralea corylifolia* suppressed papain-like protease (Kim et al., 2014a). The investigation by Schwarz et al. (2014) noticed that juglanin prevents the SARS-CoV 3a channel with an IC_{50} value of 2.3 μM. Among the NIH clinical collection of 727 tested antiviral activity compounds against both murine and human coronavirus, alkaloid macetaxine (homoharringtonine) was perhaps the most effective (Cao, Forrest, & Zhang, 2015). On the other side, Quercetin, Quercetrin, Rutin, Cinanserin (1 and 2 dpi) isolated from *H. cordata* reported showed significant against CoV murine at 15.63–500 μg/ml (Chiow et al.,

2016). Note that the SARS-CoV spike protein (S) uses ACE2 as a responsive binding site to invade host cells (Li, 2016).

In contrast, broussochalcone B, broussochalcone A, 4-hydroxyisolonchocarpine, papyriflavonol A, 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol A, broussoflavan A, kazinol F, and kazinol J extracted from *Broussonetia papyrifera* suppressed both SARS-CoV 3CLpro and PLpro, during which papyriflavonol A had the highest inhibition toward PLpro with an IC_{50} value of 3.7 μM (Park et al., 2017). Likewise, 7-methoxycryptopleurine (IC_{50}: 20 nM) was much more efficient than tylophorine (IC50: 58 nM). In another investigation, tylophorine was also identified to approach viral replication of RNA and cellular JAK2-mediated dominant NF-B activation in CoV at 0–1000 nM (Yang et al., 2017). In comparison, silvestrol impeded cap-dependent viral mRNA translation of HCoV-229E with an IC_{50} of 40 nM at 0.6–2 μM, and ouabain decreased both viral titers and viral yields and decreased the incidence of viral RNA copies at 0–3000 nM (Muller et al., 2018; Yang et al., 2020). New reports have shown that tetrandrin, fangchinoline, and cepharanthin, significantly inhibit initial phase viral-induced cell death in HCoV-OC43-infected human MRC-5 lung cells with IC_{50} values of 0.33, 1.01, and 0.83 μM, respectively (Kim et al., 2019). Also, lycorin, berbamine, emetin and mycophenolate mofetil were shown to intervene against HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59 at 0–5 μM. Lycorin and emetin suppressed cell division and hindered RNA, DNA, and protein synthesis, respectively while mycophenolate mofetil conferred an immune suppression effect on CoV species (Shen et al., 2019).

The docking studies analysis was used to examine the binding affinity and type of interaction among all compounds (67 natural molecules) and the target (Coronavirus (2019-nCoV) main protease). The outcomes of molecular modeling shown that among 67 molecules of biological origin crocin, digitoxigenin, and b-eudesmol act as inhibitors against the Coronavirus based on the energy types of interaction molecules (Aanouz et al., 2020). Also, 3CLpro sequence SARS-CoV-2 was assessed; its 3D homology model was developed and examined against a medicinal plant library containing 32,297 potential antiviral phytochemicals/Chinese traditional therapeutic molecules. Further, 5, 7, 3′, 4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, myricitrin, methyl rosmarinate, (2S)-eriodictyol7-O-(600-Ogalloyl)-beta-D-glucopyranoside and calceolarioside B isolated from *Psorothamnus arborescens*, *Myrica cerifera*, *Hyptis atrorubens* Poit. *Phyllanthus emblica* and *Fraxinus sieboldiana* may act as anti-SARS-CoV-2 active compounds for more prioritization (Ul Qamar, Alqahtani, Alamri, & Chen, 2020).

4.2 | Human herpes viruses and medicinal plants

Numerous members of the human herpesvirus (HHV) family are mostly causative factors for various human diseases. In contrast, many HHV infections are associated with Herpes Simplex Virus (HSV-1 and HSV-2). Other members of herpes viruses that cause multiple conditions are HHV-3 (Varicella-Zoster Virus), HHV-4 (Epstein Barr virus), HHV-5 (Cytomegalovirus), HHV-6, HHV-7, and HHV-8. HSV-1 and HSV-2 have encapsulated dsDNA viruses of the family *Herpesviridae*. HSV infection causes mucosal lesions in the ocular/perioral (usually HSV-1) and genital (usually HSV-2) areas and many other body sites. HSV tends to cause lifetime infection by developing itself on the sensory neurons and thus can be reactivated by different stimuli, like sun exposure, sore throat, immune suppression, menstrual cycles, or anxiety (Fatahzadeh & Schwartz, 2007). The transmission of HSV results from direct contact with infected lesions and could occur via vertical transmission from infected mother to fetus. However, the disease is typically self-limited and can be handled with antiviral drugs. However, consequences could develop in neonates, and immunosuppressed persons lead keratoconjunctivitis and life-threatening meningitis (Arduino et al., 2008; Chentoufi & Benmohamed, 2012).

Hardly any vaccine is recommended against HSV, even though there are no effective drugs that could neutralize innate HSV infection. A few primary and metastatic conditions could be monitored by analogous like acyclovir, penciclovir, and prodrugs. Moreover, the expansion of resistance to antibiotics virus is becoming a severe problem, especially in immune-compromised patients (Morfin & Thouvenot, 2003). Therefore, the discovery of new anti-HSV agents with diverse mechanisms is significant to HSV's clinical management. Plant extracts attracted substantial attention while looking for alternative compounds with anti-herpetic activity. Intriguingly, innumerable plant-derived extracts and molecules were already known to prevent HSV replication (Table 2) (Akram et al., 2018; Li et al., 2017).

Licorice roots *of Glycyrrhiza glabra* were used to prepare a 2% topical acid cream, which contains carbenoxolone sodium. The cream was used to cure12 patients having acute oral herpetic (HSV) infections. The disease symptoms such as pain and dysphagia were resolved after applying the cream six times a day within a short span of 24–48 hr. In contrast, ulceration and lymphadenopathy were shown to cure steadily within 24–72 hr (Partridge & Poswillo, 1984). Samarangenin B extracted from the leaves of *Limonium sinense* observed suppression of HSV-1 α gene expression (Kuo et al., 2002). Further, *Artocarpus lakoocha* containing oxyresveratrol was reported to prevent early and late HSV-1 and HSV-2 viral replication phases, respectively (Chuanasa et al., 2008). Pterocarnin A compound isolated from *Pterocarya stenoptera* impeded HSV-2 from adhesion and infiltration to host cells (Cheng et al., 2004). Yatein extracted from *Chamaecyparis obtuse* substantially inhibits HSV-1 replication in HeLa cells without noticeable cytotoxic effects (Kuo et al., 2006).

In comparison, several *H. cordata* flavonoids were assessed to determine their capability to obstruct the HSV-2 replication cycle. The principal flavonoids quercetine, quercitrine, and isoquercitrine showed significant HSV-2 activity (Chen et al., 2011). Subsequent investigation assessed that the mode of action could be behind the anti-herpetic activity of *H. cordata*, like adsorption, entry, post-infection by NF-kB, and virucidal activity (Hung et al., 2015). Also, meliacin obtained from *Melia azedarach* was shown to induce TNF-α and IFN-α production and reduce HSV-2 by improving virus-induced pathogenesis in the mouse genital model of herpetic inflammation (Petrera & Coto, 2009).

Comparably, the aqueous extract from *Rhododendron ferrugineum* blackberry extract and the extract from *Myrothamnus flabellifolia*

enriched with proanthocyanidin prevented the HSV-1 infection (Danaher et al., 2011; Gescher, Kuhn, Hafezi, et al., 2011; Gescher, Kuhn, Lorentzen, et al., 2011). Glucoevatromonoside, a cardenolide from *Digitalis lanata*, alter the cellular electrochemical gradient and hinder the proliferation of HSV-1 and HSV-2 in cells (Bertol et al., 2011). The natural products from the marine ecosystem such as algae and sponges produce active metabolites with anti-HSV activity (Sagar et al., 2010; Vo et al., 2011). Houttuynoids A-E extracted from *H. cordata*, showed effective anti—HSV-1 activity (Chen et al., 2012a). Another resveratrol compound isolated from the *Veratum grandiflorum* inhibited NF-kB activation, the primary bioactive substance present in grapes, peanuts, legumes, or other plant-derived matrices and perhaps in red wine (Chen et al., 2012b).

Numerous studies documented the antibacterial activity of resveratrol against the ACV-resistant and wild-type HSV-1 and HSV-2 replication cycles in cell lines and animal studies (Faith et al., 2006; Leyton et al., 2015). Compounds like spiroketalenol ether derivatives extracted from *Tanacetum vulgare* rhizome extract served as cell entry inhibitors and apprehend HSV-1 gC and HSV-2 gG glycoproteins production (Alvarez et al., 2015). Essential oils derived from *Glechon spathulata* and *Glechon marifolia* noted antiviral activity against HSV-1, which became effective after infecting Vero cells (Venturi et al., 2015). Furthermore, essential oils derived from plants of the families *Labiatae* and *Verbenaceae* have an antiviral effect on HSV. Vero cells after incubation with HSV and essential oils for 48–72 hr dramatically lowered viral titers of HSV-1 and HSV-2. It is important to note that their modes of action were related to the pre-infective stages (Brand et al., 2016). An analysis showed that the leaves of *Morus alba* L. exhibited antiviral properties against HSV-1 and HSV-2. Kuwanon X, a stilbene polyphenol derivative active compound found in this plant, reported antiviral activity against HSV at different phases of the infection process, preventing adsorption and penetration, and instant early and late gene expression of HSV-1, and replication of HSV-1 DNA (Ma et al., 2016).

Ethanolic extract from the *Eucalyptus camaldulensis* leaves prevents HSV-1 and HSV-2 infection during and after illness to Vero cells. Synergism was observed in cultured cells among acyclovir and ethanol extracts (Abu-Jafar & Mahmoud, 2017). Similarly, the antiviral activity of 24 new metabolites from the leaves of *Eucalyptus sideroxylon* and four new metabolites from genus *Eucalyptus* were reported. In contrast to HSV-1 and HSV-2 these compounds suppressed hepatitis A, coxsackie, and adenoviruses. Notably, antiviral activity against HSV-2 was exhibited by inhibiting the entrance of viruses and consequent infection processes (Okba et al., 2017). Xanthotoxin, bergapten, imperatorin, phellopterin, isoimperatorin, imperatorin, and phellopterin isolated from dichloromethane fruit extract of *Angelica archangelica* were explored as the practicable antiviral agents toward HSV l. Imperatorin and phellopterin showed the highest effect, minimizing replication of HSV-1 by 5.61 logs and 4.7 logs, respectively. The extract resulted in a decrease in the titer of the virus concerning the control of the virus. The findings demonstrate that coumarins of *A. archangelica* may be an excellent material for the formation of an alternative natural anti-HSV-1 compound (Rajtar et al., 2017).

Further, 12 compounds isolated from *Eucalyptus globulus* leaves and twigs were noticed to have antiviral efficacy against HSV-1 and HSV-2. Tereticornate A has been assessed to holds the most incredible action against HSV-1, relatively high than acyclovir. Cypellocarpin C showed significant antiviral activity against HSV-2, higher than that offered by acyclovir (Brezáni et al., 2018). Organic extracts relating to the *Peganum harmala* species showed antiviral activity against HSV-2 by disrupting virus entry (Benzekri et al., 2018). Besides, Yatein separated from *C. obtuse* prevents HSV-1 alpha gene expression, along with ICP0 and ICP4 expression of genes, by halting HSV-1 DNA replication and structural protein expression in HeLa cells (Wang et al., 2019). Natural anti-HSV substances' availability should provide novel pharmacological properties against the virus for future use in monitoring HSV infections.

4.3 | Medicinal plants in viral hepatitis

Viral hepatitis or inflammation of the liver is associated with several different viruses called hepatitis A, B, C, D, and E. Since exposure to any of these viruses results in acute infection, type B and C are distinctive in inducing chronic conditions.

4.3.1 | Hepatitis B virus

Hepatitis B virus (HBV) a prototype virus belonging to *Hepadnaviridae* family, is an enveloped virus with a relaxed circular and partly double-stranded DNA genetic structure (dsDNA) (Liang, 2009). HBV induces hepatitis B and is transmitted by contact with the virus-containing blood or other body fluids. Though some spontaneous recovery following acute hepatitis B is prevalent, due to the extreme risk of cirrhosis, HCC therapy is advised for chronic infection. The HBV vaccine design and the national vaccination policy against hepatitis B in endemic regions like Taiwan have helped to alleviate HBV infection and decreased the prevalence of HCC in the childhood stage (Ni & Chen, 2010).

Given the availability of effective vaccinations, the existing HBV compromised population remains at the threat of end-stage liver diseases, mostly in areas where vaccine schedules are inaccessible. Nucleotide/nucleoside analogs like lamivudine, adefovir, tenofovir, telbivudine, entecavir, and the immune modulator pegylated interferon-α (Peg-IFN-α) were used for the treatment of HBV infections (Kwon & Lok, 2011). Nevertheless, it is difficult to eradicate HBV from the body once a prolonged inflammation occurs. The condition gets exacerbated by threats of selecting drug-resistant viral mutants, failure of diagnosis in non-responders, and possible future viral recurrence. Thus, anti-HBV drugs' development will always be of significance for the scientific attention and hepatitis B management system's assistance to diagnose about 300–400 million carriers globally (Franco et al., 2012).

Phyllanthus species are considered an essential source of antiviral bioactive metabolites such as lignans, including hypophyllanthine and

TABLE 2 List of the potent extracts and bioactive compounds that inhibit herpes simplex virus

Plant name	Natural product(s) evaluated	Virus assessed	Culture /Animal model assessed	Proposed mechanism	References
Peganum harmala (Wild rue)	Harmine	HSV-2	In vitro	Inhibition of viral entry	Benzekri et al., 2018
Melia azedarach (Chinaberry tree)	Meliacine (Glycopeptide)	HSV-1 and HSV-2	In vitro and in vivo	Undefined	Petrera & Coto, 2009; Barquero et al., 1997
Avicennia marina	Polyphenol	HSV-1	In vitro	Inhibit replication of HSV after entry	Namazi et al., 2014
Labiatae and Verbenaceae families (essential oils)	Unknown	HSV-1 and HSV-2	In vitro	Virucidal, inhibition of viral binding, inhibition of viral entry	Brand et al., 2016
Glechon spathulata	Bicyclogermacrene	HSV-1	In vitro	Inhibition after viral attachment	Venturi et al., 2015
Glechon marifolia	Bicyclogermacrene	HSV-1	In vitro	Inhibition after viral attachment	Venturi et al., 2015
Aglaia odorata (Chinese perfume plant), *Moringa oleifera* (Moringa) and *Ventilago denticulata*	Unknown	HSV-1	In vivo	Inhibition after viral attachment	Lipipun et al., 2003
Morus alba (white mulberry)	Kuwanon X	HSV-1 and HSV-2	In vitro	Inhibition of early stages of viral infection	Ma et al., 2016
Houttuynia cordata (fish mint)	Quercitin, Isoquercitrin, and Quercitrin	HSV-1 and HSV-2	In vitro	Inhibition of NF-kB activation, inhibition of viral binding, inhibition of viral entry	Chen et al., 2011 and Hung et al., 2015
Veratum grandiflorum	Resveratrol	HSV-1 and HSV-2	In vitro	Inhibition of viral replication	Faith et al., 2006; Leyton et al., 2015
Eucalyptus camaldulensis (River Red Gum)	Unknown	HSV-1 and HSV-2	In vitro	Inhibition before and after virus adsorption	Faith et al., 2006; Leyton et al., 2015
Eucalyptus sideroxylon (Mugga)	Unknown	HSV-1 and HSV-2	In vitro	Virucidal, inhibition of viral entry, post-infection antiviral effects	Abu-Jafar & Mahmoud, 2017
Eucalyptus globulus (SouthernBlue gum)	Tereticornate A. Cypellocarpin C	HSV-1 and HSV-2	In vitro	Undefined	Brezáni et al., 2018
Cassia stipulacea (Quebracho) and *Escallonia illinita* (Ñipa)	Unknown	HSV-1	In vitro	Inhibition after virus adsorption	Pacheco et al., 1993
Aristotelia chilensis (Chilean Wineberry), *Drymis winteri* (Winter's Bark), *Elytropus chilensis* (Quilmay) and *Luma apiculata* (Chilean Myrtle)	Unknown	HSV-2	In vitro	Inhibition after virus adsorption	Pacheco et al., 1993
Quillaja saponaria (soap bark tree)	Unknown	HSV-1	In vitro	Virucidal, inhibition of virus binding, inhibition of virus entry	Roner et al., 2007
Melaleuca alternifolia (tea tree)	Unknown	HSV-1 and HSV-2	In vitro	Inhibition of virus binding, inhibition of virus entry	Garozzo et al., 2009
Melissa officinalis (Balm Mint)	Unknown	HSV-2	In vitro	Undefined	Allahverdiyev et al., 2004
Alpinia officinarum (Lesser Galangal) and *Geum japonicum* (Asian herb Bennet)	Unknown	HSV-1	In vitro	Inhibition after virus adsorption	Kurokawa et al., 1995
Alternanthera philoxeroides (Alligator weed)	Chikusetsusaponin IV	HSV-1 and HSV-2	In vitro	Virucidal	Rattanathongkom et al., 2009

TABLE 2 (Continued)

Plant name	Natural product(s) evaluated	Virus assessed	Culture /Animal model assessed	Proposed mechanism	References
Carissa edulis Vahl.	Unknown	HSV-1 and HSV-2	In vitro and in vivo	Delayed the onset of HSV infections	Tolo et al., 2006
Paeonia suffruticosa (Mudan), *Phellodendron amurense* (Amur Cork tree), *Polygala tenuifolia* (Yuan Zhi), *Polygonum cuspidatum* (Asian Knotweed), *Rhus javanica* (Java Brucea), *Syzygium aromaticum* (clove), *Terminalia arjuna* (Arjun tree) and *Terminalia chebula* (Black Myrobalan)	Unknown	HSV-1	In vitro and in vivo	Inhibition after virusadsorption	Kurokawa et al., 1995
Phyllanthus urinaria L.	1346TOGDG and geraniin	HSV-1 and HSV-2	In vitro	Undefined	Yang et al., 2007
Rheum palmatum	Aloe-emodin	HSV-1 andHSV-2	In vitro	Prevention of virus adsorption and subsequent replication	Sydiskis et al., 1991
Artocarpus lakoocha (Heartwood)	Oxyresveratrol	HSV-1 and HSV-2	In vitro	Inhibition of viral replication and late protein synthesis	. Chuanasa et al., 2008
Melia azedarach L.	Tetranortriterpenoid 1-cinnamoyl-3,11-dihydroxymeliacarpin (CDM	VSV HSV-1	In vitro	CDM modulates the NF-κB signaling pathway by lowing down its activation in HSV-1-infected conjunctival cells	Zhang et al., 2007
Limonium sinense	Samarangenin B	HSV-1	In vitro	Inhibit HSV-1 α gene expression and by arresting HSV-1 DNA synthesis and structural protein expression in Vero cells	Kuo et al., 2002
Prunella vulgaris	Lignin–carbohydrate complex (PPS-2b)	HSV-1 HSV-2	In vitro and in vivo	Block HSV-1 binding and inhibiting penetration into Vero cells	Zhang et al., 2007
Scoparia dulcis L.	Scopadulcic acid B	HSV-1	In vitro and in vivo	Inhibit the viral replication	Hayashi et al., 1988
Tanacetum vulgare	Spiroketalenol ether derivative	HSV-1 HSV-2	In vitro		Alvarez et al., 2015
Rhus aromatic	Unknown	HSV-1 and HSV-2	In vitro	Undefined	Reichling et al., 2009
Arisaema tortuosum	Apigenin and luteolin	HSV-1 and HSV-2	In vitro	Inhibition of both early and late events of the HSV-2 replicative cycle	Rittà et al., 2020
Pterocarya stenoptera	Pterocarnin A	HSV-2	In vitro	Inhibits adsorption, penetration and multiplication of HSV2 into cells	Cheng et al., 2014
Cassia javanica	ent-Epiafzelechin-(4α → 8)-epiafzelechin	HSV-2	In vitro	Inhibits viral replication	Cheng et al., 2006c
Phyllanthus urinaria	Hippomanin A	HSV-2	In vitro	Prevented HSV-2 from penetrating the cell and also interfered with HSV-2 replication at the late stage of its life cycle	Yang et al., 2007

(Continues)

TABLE 2 (Continued)

Plant name	Natural product(s) evaluated	Virus assessed	Culture /Animal model assessed	Proposed mechanism	References
Phyllanthus urinaria	Excoecarianin	HSV-2	In vitro	Inactivation of virus particles	Cheng et al., 2011
Terminalia chebula	Chebulagic acid and punicalagin	HSV-1	In vitro	Cell surface GAG competitors; inhibit viral entry (binding and fusion) and post infection cell-to-cell spread	Lin et al., 2011
Melia azedarach	Meliacine	HSV-2	In vivo	Induces TNF-α and IFN-γ production	Petrera et al., 2009
Houttuynia cordata	Houttuynoids A-E	HSV-1	In vitro	Undefined	Chen et al., 2012a
Rhododendronferrugineum L.	Unknown	HSV-1	In vitro	Inhibits viral adsorption and penetration	Gescher et al., 2011a
Blackberry extract	Unknown	HSV-1	In vitro	Inhibits viral replication and exhibits virucidal activity	Danaher et al., 2011
Myrothamnus flabellifolia	Proanthocyanidin-enriched extract	HSV-1	In vitro	Inhibits viral adsorption and penetration steps	Gescher et al., 2011a
Digitalis lanata	Glucoevatromonoside	HSV-1	In vitro	Inhibits viral protein synthesis	Bertol et al., 2011
Schinus terebinthifolia	Catechin	HSV-1	In vitro	Effective in the attachment and penetration stages	Nocchi et al., 2017
Cornus canadensis	Tellimagrandin I	HSV-1	In vitro	Undefined	Lavoie et al., 2017
Hemidesmus indicus	2-Hydroxy-4- methoxybenzaldehyd; 3-hydroxy-4-methoxybenzaldehyde	HSV-1 and HSV-2	In vitro	Anti-ER α-glucosidase inhibitory activity	Bonvicini et al., 2018
Equisetum giganteum and *Copaifera reticulate*	Unknown	HSV-2	In vitro and in vivo	Interfering with viral cell attachment and entry	Churqui et al., 2018
Punica granatum L.	Punicalagin	HSV-2	In vitro	Undefined	Arunkumar & Rajarajan, 2018
Peganum harmala L.	Harmine	HSV-2	In vitro	Undefined	Benzekri et al., 2018
Erythrina speciosa	Vitexin	HSV-1	In vitro	Undefined	Fahmy et al., 2020

phyllanthine, flavonoids (ternatin), and alkaloids such as quercetin. They can block the endogenous DNA polymerase enzyme of HBV, which is crucial for viral replication (Venkateswaran et al., 1987). A variety of bioactive metabolites extracted from *Phyllanthus niruri* were also evaluated for their inhibitory potential, using sera containing HBsAg, collected from chronic HBV patients (Thyagarajan et al., 1982). Subsequent studies have revealed the in vivo efficiency of *P. niruri* extract in eliminating HBV in 3–6 weeks in mammals. A 90-day treatment with plant extracts successfully reduced the HBV antigen to undetectable levels among two-thirds of HBV-positive patients (Wang et al., 1995). Further, numerous studies were conducted in the last several years to recognize anti-HBV molecules from medicinal herbs (Cui et al., 2010; Qiu et al., 2013; Zhan et al., 2010; Zhang et al., 2010). For examples, the antiviral effects of the saikosaponins from *Bupleurum* species and the ethanol extract from *Polygonum cuspidatum* were reported against HBV in vitro (; Chang et al., 2007; Chang et al., 2005). Further, curcumin showed to suppress the HBV gene's replication and an appearance by controlling the peroxysome proliferator-activated gamma receptor co-activator 1-alpha (PGC-1α), the HBV transcription co-activator (Rechtman et al., 2010). Furthermore, *Phyllanthus*, *Salvia miltiorrhiza*, *Rheum palmatum* L., and *Radix astragali* and chemical compounds like oxymatrine, artemisinin, artesunate, and wogonin also reported promising anti-HBV activities (Cui et al., 2010). Other examples include isochlorogenic acid A, amide alkaloid, and dehydrocheilanthifoline from *Laggera alata*, *Piper longum*, and *Corydalis saxicola* experienced high anti-HBV activities (Hao et al., 2012; Jiang et al., 2013; Zeng et al., 2013). The LPRP-Et-97,543, isolated from the roots of *Liriope platyphylla*, hinders the mechanism of HBV's action by regulating the gene expression and the DNA replication by viral proteins by interacting with the pathway of NF-αB nuclear factor (Huang et al., 2014).

There seems to be a lack of studies on bioactive components' mode of action against HBV, while most natural compounds were proven to effectively suppress the HBV (Wu, 2016) (Table 3). For instance, *Acanthus ilicifolius* L. significantly decreases HBV-induced liver damage by lowering the transaminase (Wei et al., 2015). *Gymnema sylvestre* phytoconstituents prevent HBsAg binding and HBV DNA polymerase activity (Subashini and Rajendran, 2015). Further, the expression of intracellular HBV DNA in HBV WT-or mutant-transfected HepG2 cells declined following *Phyllanthus* extract treatment. *Phyllanthus* triggered interferon-beta, cyclooxygenase-2, and interleukin-6 mRNA expression in HBV WT-transfected HepG2 cells, probably by modulation of extracellular signal-regulated kinases and c-jun N-terminal kinases and by induction of retinoic acid-inducible gene-I, toll-like receptor 3, myeloid distinctions of primary response gene, and tumor necrosis of fac (Jung et al., 2015). Two new major C-boivinopyranosyl flavones (luteolin-6-C-β-D-boivinopyranosyl-3′-O-β-D-glucopyranoside and chrysoeriol-6-C-β-boivinopyranosyl-4′-O-β-D-glucopyranoside) isolated from *Alternanthera philoxeroids* showed substantial anti-HBV activity by reducing HBsAg secretion in HepG2.15 cells (Li et al., 2016).

Consequently, ethanol extract of *Sanguisorba officinalis* and its significant compounds (ziyuglycoside I and II) against HBV in HepG2.2.15 cells inhibit replication and antigen secretion of HBV. Hence, describing the plant's tendency as novel candidates for the treatment of HBV-related diseases (Jang et al., 2018). The anti-HBV effect of *Abrus cantoniensis* were explored both in vitro and in vivo studies. Treatment of *A. cantoniensis* strongly suppressed the development of HBV DNA, Hepatitis Be Antigen (HBeAg), and Hepatitis B surface antigen (HBsAg) in HepG2.2.15 cells and rAAV8-1.3HBV transfected mice, which provides a base for its possible clinical usage (Yao et al., 2020). Quercetin and myricetin-3-O-rhamnoside extracted from *Guiera senegalensis* leaves showed antiviral activity (HBsAg and HBeAg assay) in HepG2.2.2.15 HBV-reporter cells. Quercetin notably repressed HBsAg and HBeAg synthesis by approximately 60 and 62%, respectively, compared to myricetin-3-O-rhamnoside by 44 and 35%. Their probable anti-HBV mode of action was expected by the ability to bind with viral Pol/RT and core as well as host NTCP proteins (Parvez et al., 2020).

Furthermore, the HBV inhibition activities of polysaccharide from *Radix isatidis* were mediated by the stimulation of the IFN-α-dependent JAK/STAT signal pathway and the initiation of protein expression against HBV (Wang et al., 2020). Swertisin obtained from *Iris tectorum* displayed a significant inhibitory effect for HBV replication by inhibiting HBeAg and HBsAg and HBV DNA (Xu et al., 2020). Although novel anti-HBV inhibitors were developed, the combination of remedies with conventional nucleotide/nucleoside analogs or IFN-α-based hepatitis B therapy must also be assessed in future research.

4.3.2 | Hepatitis C virus

HCV is a flavivirus with a positive-sense ssRNA, usually transmits through blood-to-blood interactions, intravenous injections, blood transfusion, and varying exposures to blood toxic substances. Due to the overly abstract nature of HCV, a precautionary vaccine has not been available yet. Approximately 70% of infections are consistent, affecting an estimated 300 million carriers worldwide, among which 1–3% can proceed to end-stage liver diseases, such as cirrhosis and HCC (El-Serag, 2012). The recommended treatment comprises Peg-IFN-α plus oral ribavirin parenteral. Nevertheless, few challenges exist in the current method of HCV treatment. They have limited efficacy for specific viral genetic variants, unavoidable selection of drug-resistant mutants, adverse side effects, exorbitant prices of medication, patient adherence issues, and challenges in diagnosing communities such as non-responsive patients and patients with liver transplantation (Welsch et al., 2012). The rapid expansion of anti-HCV substances is indeed essential to address such deficiencies.

Table 3 summarizes the antiviral potential of different natural products determined against HCV infection. For instance, *Silybum marianum* and its flavonolignans showed significant anti-HCV activity in vitro (Polyak et al., 2007, 2010). Many clinical trials showed a viable impact on reducing the viral load (Marino et al., 2013; Neumann et al., 2010). Curcumin was reported as a critical inhibitor of HCV replication by conceivably restricting the sterol regulatory element-binding to protein-1 (SREBP-1)-Akt pathway Kim et al., 2010), and its

TABLE 3 Antiviral effects from several potent natural products/extracts against specific viruses

Natural products/Extracts evaluated	Virus strain assessed	Culture/Animal model assessed	Proposed mechanism	References
Isochlorogenic acid A (*Laggera alata*)	HBV	HepG2.2.15 cells	Blocking the translation step of the HBV replication and reducing the stability of the HBV core protein and thus blocking the refill of nuclear HBV cccDNA	Hao et al., 2012
Amide alkaloid (*Piper longum*)	HBV	HepG2.2.15 cells	Undefined	Jiang et al., 2013
Dehydrocheilanthifoline (*Corydalis saxicola)*	HBV	HepG2.2.15 cells	Inhibits the replication of HBV	Zeng et al., 2013
Saikosaponins (C, D) (*Bupleurum* species)	HBV	HepG2.2.15 cells	Saikosaponin C inhibits HBeAg expression and HBV DNA replication	Chiang et al., 2003
Ethanol extract (*Polygonum cuspidatum*)	HBV	HepG2.2.15 cells	Inhibits the expression of HBeAg	Chiang et al., 2005
Curcumin	HBV	HepG2.2.15 cells	Viral transcription suppressor via down regulation of the co-activator PGC-1α	Rechtman et al., 2010
Glycyrrhizinic acid (*Glycyrrhiza glabra*)	HBV	HepG2.2.15 cells	Undefined	Pompei et al., 2009
Artemisinin (*Artemisia annua*)	HBV	HepG2.2.15 cells	Inhibition of viral production	Efferth et al., 2008
Root extract (*Boehmeria nivea*)	HBV	HepG2 2.2.15 cells	Inhibition of viral production	Huang et al., 2006
Ethanol extract (*Polygonum cuspidatum*)	HBV	HepG2 2.2.15 cells	Inhibition of viral production	Chang et al., 2005
LPRP-Et-97,543 (*Liriope platyphylla*)	HBV	HepG2 2.2.15 cells	Inhibit viral gene expression and replication. Inhibit viral promoter activity	Huanga et al., 2014
1,2,3,4,6-penta-O-galloyl-beta-D-glucoside (*Saxifraga melanocentra* Engl.& Irmsch)	HCV	COS-7 fibroblast-like cells	Inhibition against HCV NS3 serine protease	Zuo et al., 2005
Standardized Silymarin extracts (*Silybum marianum*)	HCV	Human hepatoma-derived (Huh7 and Huh7.5.1) cells	Antiviral effect partly due to enhancement of the IFN-associated JAK–STAT pathway	Polyak et al., 2007
Flavonolignans (*Silybum marianum/silymarin*)	HCV	Huh7 cells	Antiviral effect probably related to antioxidant functions of the flavonolignans	Polyak et al., 2010
Curcumin	HCV	Huh7 cells	HCV replication inhibitor via suppressing Akt-SREBP-1 pathway	Kim et al., 2010
Epigallocatechin-3-gallate	HCV	Huh7 cells	Inhibits viral entry by affecting the fluidity of the HCV envelope; inhibits viral entry	Ciesek et al., 2011; Calland et al., 2012
Griffithsin	HCV	Huh7 cells	Prevents infection and inhibits viral cell-to-cell transmission	Meuleman et al., 2011
Ladanein	HCV	Primary human hepatocytes	Inhibits viral entry	Haid et al., 2012
Tellimagrandin I (*Rosae Rugosae*)	HCV	Huh7 cells	HCV invasion inhibitor	Tamura et al., 2010
Chebulagic acid and punicalagin (*Terminalia chebula* Retz.)	HCV	Huh-7 cell	Inactivate free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread	Lin et al., 2013
Saikosaponin b2 (*Bupleurum kaoi*)	HCV	Huh-7 cells	Inhibiting early HCV entry, including neutralization of virus particles, preventing viral attachment	Lin et al., 2015
Chalepin and pseudane IX (*Ruta angustifolia*)	HCV	Huh-7 cells	Inhibited HCV at the post-entry step and decreased the levels of	Wahyuni et al., 2014

TABLE 3 (Continued)

Natural products/Extracts evaluated	Virus strain assessed	Culture/Animal model assessed	Proposed mechanism	References
			HCV RNA replication and viral protein synthesis	
Elderberry liquid extract (*Sambucus nigra*)	IFA and IFB	Madin–Darby canine kidney (MDCK) cells	Unclear	Krawitz et al., 2011
EPs® 7,630 (Umckaloabo®) Root extract (*Pelargonium sidoides*)	IFA	MDCK cells	Inhibits viral entry and release; inhibits viral hemagglutination and NA activity	Theisen et al., 2012
Aqueous extract (*Taraxacum officinale*)	IFA	MDCK cells	Inhibits viral NP RNA levels and polymerase activity	He et al., 2011
Spirooliganone B (*IlliciumOligandrum*)	IFA	MDCK cells	Undefined	Ma et al., 2013
Chalcones (*Glycyrrhiza inflate*)	IFA	MDCK cells	IFA NA inhibitors	Dao et al., 2011
Xanthones (*Polygala karensium*)	IFA	MDCK cells	IFA NA inhibitors	Dao et al., 2011
Homoisoflavonoids (*Caesalpinia sappan*)	IFA	MDCK cells	IFA NA inhibitors	Jeong et al., 2012
Quercetin 3rhamnoside (*Houttuynia cordata*)	IFA WS/33 virus	MDCK cells	Inhibit replication in the initial stage of virus infection by indirect interaction with virus particles	Choi et al., 2009
Geranium sanguineum	IFA	MDCK cells/male and female (16Ð18 g), inbred ICR mice	Undefined	Pantev et al., 2006
Elderberry extract	IFA and IFB	60 adult influenza patients	Undefined	Zakay-Rones et al., 2004
Taxodium distichum	IFA and IFB	MDCK cells	Inhibited viral entry and budding; blocked neuraminidase activity	Hsieh et al., 2016
CYSTUS052 (*Cistus incanus*)	IFA (H7N7)	MDCK cells	Undefined	Droebner et al., 2007
Water extract (*Panax notoginseng*)	IFA	MDCK, YAC-1, and RAW 264.7 cells	Undefined	Choi et al., 2017
Aurantiamide acetate (*Baphicacanthus cusia*)	IFA	MDCK cells	Inhibition of the NF-κB pathway	Zhou et al., 2017
Isocorilagin (*Canarium album*)	IFA	MDCK cells	Inhibited neuraminidase activity	Chen et al., 2020
Jatropha multifida	IFA	MDCK cells	Undefined	Shoji et al., 2017
Ethanol extract (*Geranii Herba*)	IFA	MDCK cells	Inhibited neuraminidase activity	Choi et al., 2019
Polyphenols (*Avicennia marina*)	HIV-1	Human embryonic kidney cells (HEK293)	Undefined	Namazi et al., 2014
Soulattrolid (*Calophyllum teysmannii*)	HIV-1 and HIV 2	CEM-SS cells	Undefined	Pengsuparp et al., 1996
Phyllanthus amarus and Olive leaf extract	HIV-1 and HIV 2	MT4 and MOLT3 cell lines	Inhibits HIV replication both in vitro and in vivo	Notka et al., 2004
Artemisia annua and *Artemisia afra*	HIV-1	HeLa cells	Undefined	Lubbe et al., 2012
Tricyclic coumarin (*Calophyllum brasiliense*)	HIV-1	U1 and Molt-4 cell lines	Inhibits viral replication in both acute and chronic infections by suppressing NF-κB	Kudo et al., 2013
Patentiflorin A (*Justicia gendarussa*)	HIV-1	Undefined	Inhibits NRTI (nucleoside reverse transcriptase inhibitor)-resistant isolate (HIV-11617-1) of the analog (AZT) as well as the NNRTI (non-nucleoside reverse transcriptase inhibitor)-resistant isolate (HIV-1N119) of the analog (nevaripine).	Zhang et al., 2017a, 2017b
	HIV-1	LC5-RIC cells		Helfer et al., 2014

(Continues)

TABLE 3 (Continued)

Natural products/Extracts evaluated	Virus strain assessed	Culture/Animal model assessed	Proposed mechanism	References
Root extract (*Pelargonium sidoides*)			Interferes directly with viral infectivity and blocks the attachment of HIV-1 particles to target cells, protecting them from virus entry	
Aqueous extracts (*Cistus incanus*)	HIV-1 and HIV 2	LC5-RIC	Preventing primary attachment of the virus to the cell surface and viral envelope proteins from binding to heparin	Rebensburg et al., 2016
Rhusflavanone (*Rhus succedanea* and *Garcinia multiflora*) as well as their methyl ethers and acetates	MV	Vero cell lines	Undefined	Lin et al., 1996
Calcium spirulan (*Spirulina platensis*)	MV	Vero cell lines	Undefined	Hayashi et al., 1996
Zanthoxylum chalybeum and *Warburgia ugandensis*	MV	Vero cell lines	Undefined	Olila et al., 2002
Olinia rochetiana and *Warburgia ugandensis*	MV	U937 cell lines	Neutralize virus particles	Parker et al., 1997
Stem and root extract (*Cajanus cajan*)	MV	Hep-2 cell lines	Inhibited MV replication, as indicated by the absence of CPE at higher extract concentrations	Nwodo et al., 2011
Chebulagic acid and punicalagin (*Terminalia chebula*)	MV	CHO-SLAM	Inactivate free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread	Lin et al., 2013
Chebulagic acid and punicalagin (*Terminalia chebula*)	RSV	HEp-2 cells	Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell	Lin et al., 2013
Uncinoside A and B (*Selaginella uncinata*)	RSV	HEp-2 cells	Undefined	Ma et al., 2003
Dicaffeoylquinic acids (*Schefflera heptaphylla*)	RSV	HEp-2 cells	Inhibition of virus–cell fusion in the early stage and the inhibition of cell–cell fusion at the end of the RSV replication cycle	Li et al., 2005b
Genkwanol B, genkwanol C, and stelleranol (*Radix Wikstroemiae*)	RSV	HEp-2 cells	Undefine	Huang et al., 2010
Flavones C-glycosides (*Lophatherum gracile*)	RSV	HEp-2 cells	Undefined	Wang et al., 2012c
Cimicifugin (*Cimicifuga foetida*)	RSV	HEp-2 and A549 cells	Inhibits viral attachment and internalization steps; stimulates IFN-β secretion	Wang et al., 2012b
Cimicifuga foetida	RSV	HEp-2 and A549 cells	Inhibits viral attachment and internalization steps; stimulates IFN-β secretion	Wang et al., 2012a
Resveratrol	RSV	BALB/c mice	Reduces virus-induced airway inflammation via down-regulation of IFN-γ levels during RSV infection	Zang et al., 2011
Chebulagic acid and punicalagin (*Terminalia chebula* Retz.)	RSV	Vero cells	Block viral entry related events, including binding and fusion	Lin et al., 2013
	RSV	HEp-2 cells	Affected the intracellular replication of RSV. Tangeretin	Xu et al., 2014

TABLE 3 (Continued)

Natural products/Extracts evaluated	Virus strain assessed	Culture/Animal model assessed	Proposed mechanism	References
Tangeretin and nobiletin (Polymethoxylated flavones) (*Citrus reticulate*)			down regulated the expression of RSV phosphoprotein (P protein)	
Ethanol extract (*Lophatherum gracile*)	RSV	HEp-2 cell line	Inhibit RSV infection and RSV-induced inflammation	Chen et al., 2019
Aqueous and ethanolic extracts; linalool, apigenin, and ursolic acid (*Ocimum basilicum*)	CVB	BCC-1/KMC cells	Ursolic acid interferes with viral infection and replication	Chiang et al., 2012
Raoulic acid (*Raoulia australis*)	CVB	Vero cells	Undefined	Choi et al., 2009
Isatindolignanoside A (*Isatis indigotica)*	CVB3	Vero cells	Undefined	Meng et al., 2018
Aqueous leaf extract (*Azidarachta indica*)	DENV-2	C6/36 cells	Undefined	Parida et al., 2000
Petroleum ether, ethyl acetate, ethyl ether and coumane (*Alternanthera philoxeroides*)	DENV	C6/36 cells	Undefined	Jiang et al., 2005
Flavonoids and cyclohexenyl (*Boesenbergia rotunda*)	DENV-2	C6/36 cells	Inhibition of dengue-2 virus NS3 protease	Kiat et al., 2006
Narasin	DENV-2	Huh-7 cells	Disrupts viral protein synthesis without affecting viral RNA replication	Low et al., 2011
Quercetin	DENV-2	Vero cells	Inhibits viral replication but not the viral attachment and entry processes	Zandi et al., 2011
Polyphenol (*Sambucus nigra*)	DENV-2	BHK-21 and VERO cells	Undefined	Castillo-Maldonado et al., 2017
Ethanol extract of leaves (*Senna angustifolia*), ethanol extract of leaves (*Tridax procumbers*), and methanol extract of leaves (*Vernonia cinerea*)	DENV-2	Vero cells	Undefined	Rothan et al., 2014
Baicalein	DENV-2	Vero cells	Virucidal activity against extracellular virus; impedes viral adsorption onto the host cell; inhibits viral replication post entry	Zandi et al., 2012
Chebulagic acid and punicalagin (*Terminalia chebula*)	DENV-2	Vero cells	Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission	Lin et al., 2013
Schisandrin (*Schisandra chinensis*)	DENV	Vero cells	Inhibits DENV replication	Yu et al., 2017
Epigallocatechin gallate (green tea)	EV 71	Vero cells	Interferes with viral replication via modulation of the cellular redox environment	Ho et al., 2009
Raoulic acid (*Raoulia australis*)	EV 71	Vero cells	Undefined	Choi et al., 2009
Gallic acid (*Woodfordia fruticosa*)	EV 71	Vero cells	Inhibition of EV71 production	Choi et al., 2010
Aqueous and ethanolic extracts; linalool, apigenin, and ursolic acid (*Ocimum basilicum*)	EV 71	BCC-1/KMC cells	Ursolic acid interferes with viral infection and replication	chiang et al., 2003
Hederasaponin B (*Hedera helix*)	EV 71	Vero cells	Inhibition of viral capsid protein synthesis	Song et al., 2014; Hong et al., 2015
Rosmarinic acid (*Melissa officinalis*)	EV 71	Vero cells	Suppresses eIF4G cleavage; removes ROS and inhibits	Chen et al., 2017

(Continues)

TABLE 3 (Continued)

Natural products/Extracts evaluated	Virus strain assessed	Culture/Animal model assessed	Proposed mechanism	References
			activation of p38 kinase, blocking hnRNPA1 translocation and EPS15 phosphorylation	
Silvestrol (*Aglaia foveolata)*	Ebola virus (EBV)	Huh-7 and VeroE6 cells	a specific eIF4A helicase inhibitor	Biedenkopf et al., 2016
Curcumin (*Curcuma longa*)	EBV	Vero cells	Interaction with VP30 (based on docking data)	Mathew and Hsu, (2018)
Phytol, aloe-emodin, byzantionoside B, a mixture of *trans*-martynoside and *cis*-martynoside, a mixture of *trans*-isomartynoside and *cis*-isomartynoside, luteolin-7-*O*-*β*-D-glucopyranoside, and apigenin-7-*O*-[*β*-D-apiofuranosyl (1→6)-*β*-D-glucopyranoside *(Lindernia crustacean)*	EBV	Burkitt's lymphoma cell line (P3HR)	Undefined	Tsai et al., 2020

adverse impact on HCV entry (Anggakusuma et al., 2013). Many natural products deter HCV entry, including epigallocatechin-3-gallate, griffithsin, ladanein, and tellimagrandin I (Calland et al., 2012; Ciesek et al., 2011; Haid et al., 2012; Meuleman et al., 2011; Takebe et al., 2013). Similarly, chebulagic acid and punicalagin hydrolyzable tannins were found as competitive HCV intake inhibitors (Lin et al., 2013). Both tannins inactivate free virus particles, inhibit viral adhesion and penetration of the host cell, and interrupt HCV cell-to-cell post-infection transfer. As the HCV immunization is unavailable, the identification of new anti-HCV entry inhibitors could help develop preventive hepatitis C therapy/medication.

Loliolide isolated from *Phyllanthus urinaria* inactivates the HCV virus and stops viral attachment and entry/fusion (Chung et al., 2016). Leaves extract and fractions of *Ficus fistulosa* using Huh7it cells and HCV JFH1a inhibited HCV JFH1a with an IC_{50} value of 20.43 ± 4.51 μg/ml (Hafid et al., 2016). The dichloromethane extract of *Artocarpus heterophyllus* demonstrated good anti-HCV activity using Huh7it-1 cells with an inhibitory concentration (IC_{50}) of (1.5 ± 0.6) μg/ml. *A. Heterophyllus* impeded the viral entry process by direct virucidal activity and targeting host cells and HCV RNA replication. HCV protein expression was substantially decreased by elevated-concentration treatment (Hafid et al., 2017). Antiviral activity of methanol extract of *Ajuga bracteosa*, *Ajuga parviflora*, *Berberis lyceum*, and *Citrus lemon* against HCV infected HepG2 cells showed that 24-hour treatment with *A. parvifloras* exhibited maximum antiviral activity, accompanied by *A. bracteosa*. The findings demonstrate these as a substitute standard therapy or in combination with conventional HCV therapies to treat HCV infections (Yousaf et al., 2018). Two fractions "N1" and "N8" isolated from acetone extract of *Nymphaea alba* suppressed HCV NS3 gene expression in transfected Huh-7 cells with an EC_{50} value of 37 ± 0.03 and 20 ± 0.02 μg/ml, respectively. Besides, the combination of fractions with the standard antiviral drug showed stimulatory activity to suppress HCV replication. *N. alba* and its isolated compounds may offer a promising source regimen against HCV, alone or even in mixture with other prospective anti-HCV entities (Rehamn et al., 2018).

4.4 | HIV/AIDS and medicinal plants

Human immunodeficiency virus (HIV) is an encased lentivirus of the Retroviridae family. HIV attacks immune cells, reverses the ssRNA genome's transcription, and incorporates into the host chromosome DNA (Sierra et al., 2005). It is transmitted through an interchange of viruses containing blood and fluids, like sexual intercourse, the sharing of infected needles/sharp objects, and breastfeeding (Shaw & Hunter, 2012). HIV is the principal cause of acquired immunodeficiency syndrome (AIDS), the gradual incompetence of the immune cells due to CD4+T lymphocyte deterioration, leading to life intimidating infectious disease and autoimmune disorders (Moss, 2013).

Amidst approximately 30 years of scientific research ever since its exploration, there's still currently no specific preventative medicine or remedy for HIV infectious diseases. The high antigenic variability and myriad pathways used by the virus to undermine the immune system's appreciation have made prophylactic/therapeutic management of HIV infection complicated (Burton et al., 2004). Interestingly, the development of highly active antiretroviral therapy (HAART), consisting of a cocktail of nucleoside analog/non-nucleoside reverse transcriptase inhibitors, has significantly decreased the mortality rates associated with HIV/AIDS (Ghosh et al., 2011). However, there is still an urgent need for adequate therapeutic approaches against HIV infection related to drug resistance development, accompanying toxicity treatment, patient adherence, and inadequate access in resource-poor areas (Piot & Quinn, 2013).

A comprehensive list of herbal ingredients for HIV infection was examined (Cos et al., 2008; Singh & Bodiwala, 2010) (Table 3). In contrast, marine products with anti-HIV activity were reported as potential anti-HIV treatment (Kim et al., 2011; X. Zhou et al., 2013). *Phytolacca americana* is a potent source of a set of plant proteins known as pokeweed antiviral protein (PAP). Three isoforms, specifically from spring leave PAP-I, early summer leaves PAP-II, and late summer leaves PAP-III was identified as a class of ribosome-inactivating proteins (RIPs) responsible for causing depurination of genomic HIV-1 RNA (Rajamohan et al., 1999). Similarly, *Momordica charantia* and *Gelonium multiflorum* are considered useful sources of an anti-HIV protein MAP30 and GAP31, similar to RIPs known for their anti-HIV potency (Schreiber et al., 1999).

Furthermore, the leaves of *P. americana* also contain an anti-HIV protein PAP29, having a prophylactic anti-HIV potential. P. Wang and Tumer (1999) reported that PAP isolation cleaves supercoiled DNA into linear and straightforward forms using the same active site required to remove rRNA purine. The RIPs are toxic N-glycosidases that purify the typically preserved α-sarcin loop of large rRNAs. Thus, depuration disables the ribosome, consequently obstructing its further involvement in protein synthesis. Several studies have shown that RIP's enzymatic activity is not only restricted to site-specific activity on ribosome rRNAs but also entails the depuration and nucleic acid scission of other targets (Barbieri et al., 2000; Horrix et al., 2011; Nicolas et al., 1998). Trichobitacin, a RIP, extracted from the roots of *Trichosanthes kirilo*wiiis was reported to decline the appearance of the p24 HIV-1 antigen by reducing the number of antigens in HIV-positive cells in an acute in vitro assay but failed in cases of chronic infection (Zheng et al., 2000). Cyanovirin-N extracted from marine algae showed an inhibitory effect on HIV through aborting transmission and cell to cell fusion of HIV by interacting strongly with gp120 (De Clercq, 2000). Several sulfated polysaccharide groups extracted from seaweeds possess anti-HIV effects by interfering with viral adsorption (Duarte et al., 2001; Schaeffer & Krylov, 2000). Alkaloid extracts of *P. niruri* exhibited an inhibitory effect on HIV by monitoring the inhibition of HIV-induced cytopathogenecity in human MT-4 cells (Naik & Juvekar, 2003). Furthermore, coumarin-containing calophyllum species exhibited an inhibitory effect on HIV (Cesar et al., 2011; Huerta-Reyes et al., 2004). Similarly, the crude extracts of *A. annua* and *Artemisia afra* revealed promising anti-HIV efficacy (Lubbe et al., 2012). In regards, tricyclic coumarin reported from *Calophyllum brasiliense* stem bark suppressed HIV replication by repressing the activation of nuclear factor-kappa B (NF-κB) in in vitro models (Kudo et al., 2013).

The root extract of *Pelargonium sidoides* displays potent anti-HIV-1 activity by protecting peripheral blood mononuclear cells and macrophages from infection with several X4 and R5 tropic HIV-1 strains. Thus, it is considered a novel herbal medicine for anti-HIV-1 therapy with different action mechanisms and complementary to current single-molecule drugs (Helfer et al., 2014). Furthermore, *Cistus incanus* inhibited clinical HIV-1 and HIV-2 isolates in vitro, and no resistant viruses appeared throughout 24 weeks of continuous propagation of the virus in the presence of *C. incanus* aqueous extract (Rebensburg et al., 2016). Methanol extracts of *Euphorbia spinidens* Bornm (Euphorbiaceae) possess significant antioxidant activity due to high phenolics terpenes and saponins and flavonoid compounds and have a strong antiviral effect on HSV-1 by inhibiting the replication of the virus (Karimi et al., 2016; Mohammadi et al., 2014). Patentiflorin A isolated from *Justicia gendarussa*, shows significant activity against various HIV strains by acting as a potential HIV-1 reverse transcription inhibitor with IC_{50} values ranging from 15–21 nM (Zhang et al., 2017a, 2017b).

Besides this, a diverse range of medicinal plants such as *Withania somnifera* (Williams-Orlando, 2017), *Tinospora cordifolia* (Husain et al., 2017), *Moringa oleifera* (Monera-Penduka et al., 2017), *Hypericum perforatum* (Béjaoui et al., 2017), *Silybum marianum* (Lovelace et al., 2017), *Panax ginseng* (Cho & Kim, 2017), *Hypoxis hemerocallidea* (Jegede et al., 2017), *Sutherlandia frutescens* (Wilson et al., 2015), *Lobostemon trigonus* (Koffuor et al., 2014), and *Curcuma longa* (Kim et al., 2014b) were used in the diagnosis and treatment of AIDS. In comparison, four new lignans from the aerial parts of *Justicia procumbens* were examined for anti-HIV-1 activity. One of the new secoisolariciresinol dimethyl ether acetate showed significant anti-HIV-1 activity with an IC_{50} of 5.27 μM in vitro (Xu et al., 2019). Premised on the scientific advances till now, rapid advances in identifying natural antivirals against HIV must produce novel therapeutic regimens that would play a critical role in combating the existing immediacy of anti-HIV/AIDS therapeutics.

4.5 | Anti-influenza virus and medicinal plants

Influenza A, B, and C viruses (IFA, IFB, and IFC) are encapsulated negative-sense ssRNA viruses categorized in the Orthomyxoviridae family. Such viruses can cause respiratory infection with symptoms include fever, headache, sore throat, sneezing, and muscle and joint pain, which can lead to devastating and potentially lethal situations like pneumonia (Eccles, 2005; Rello & Pop-Vicas, 2009). IFA (most epidemics) has a broad array of hosts, such as birds, human beings, and other mammals. At the same time, IFB seems to harm people naturally, and IFCs could be separated from humans and pigs (Pleschka, 2013). The infection of influenza viruses has caused significant human morbidity, and approximately 250,000 to 500,000 fatalities happen yearly as a consequence of periodic epidemics. This figure was documented to rise to about 20–40 million deaths in major pandemics, as was the case with the Spanish flu of 1918 (Saunders-Hastings & Krewski, 2016).

Hemagglutinin (HA) and neuraminidase (NA) protein envelopes are developed by the IF vaccines through prior contact or immunization, thus, making any pre-existing antibody inefficient and susceptible to infection. Another concern is the pervasive growth of drug resistance, mostly M2 ion channel blockers of amantadine and rimantadine, in the first wave of anti-influenza drugs. Resistant strains of available neuraminidase inhibitors such as oseltamivir and zanamivir (which mainly prevent the release of mature influenza viruses) have also been identified (Samson et al., 2013). As a result of drug

resistance development, the rapid evolution of influenza viruses, and the incidence of many recent outbreaks (e.g., H5N1, H1N1, H7N9), more advanced antiviral strategies are urgently needed to prevent and control potential pandemics with evolving influenza strains (Shao et al., 2017). Numerous natural products have been assessed for their adverse effects on influenza (Table 3).

Pelargonium estides root extract restricts IFA entry influences, viral hemagglutination, neuraminidase function, and improves influenza-infected mice (Theisen & Muller, 2012). Aqueous extract from *Taraxacum officinale* inhibits IFA infection and reduces the activity of polymerase and nucleoproteins (NP) RNA levels (He et al., 2011). Several plant secondary metabolites were also determined as possible inhibitors of NA influenza (Grienke et al., 2012) such as chalcones from *Glycyrrhiza inflata* (Dao et al., 2011), xanthones from *Polygala karensium* (Dao et al., 2012), homoisoflavonoids from *Caesalpinia sappan* (Jeong et al., 2012), and spirooliganone B from the roots of *Illicium oligandrum* (Ma et al., 2013). Lariciresinol-4-O-D-glucopyranoside isolated from the root of *Isatis indigotica* hindered the IAV-induced pro-inflammatory response. The underpinning coping mechanism against IAV infection derives from pharmacological actions on the immune system, signal transduction, cell cycle, and metabolism (Li et al., 2015; Zhou et al., 2017). The *Sambucus nigras* activities against influenza were investigated extensively, especially in the vicinity (Roschek et al., 2009; Ulbricht et al., 2014). Studies have shown the potency of *S. nigra* toward infectious disease, which may be caused by immune system stimulation (Ho et al., 2015; Ho et al., 2016). Immunomodulating peptic polysaccharides, polyphenolic, and flavonoid of *S. nigra* are responsible for suppressing the viruses. This plant's berries and flowers are documented from diverse cultures (Porter & Bode, 2017).

The double-blind trial was conducted among 40 adults and children in southern Israel confirmed to have influenza B. The fruit of *Sambucus nigra* (black elder) syrup or placebo 1 tbsp b.i.d. (for children) or 2 tbsp b.i.d. (for adults) was given. Symptom severity and duration (mean 1.3 days shorter with black elders) were appreciably lesser in the black elder group than placebo (Zakay-Rones et al., 1995). A similar double-blind trial of 60 adult Norwegians with influenza A or B was conducted. Again, symptom severity was significantly less with black elders than placebo, and in this case, recovery was on average 4 days quicker with black elders. The use of rescue medication was also notably less in the black elder group versus placebo. There were no adverse effects in either of these trials (Zakay-Rones et al., 2004). Recently, a randomized trial of 312 Australian adults undertaking international travel by coach received black elder capsules 300 mg b.i.d. before travel and t.i.d. during travel and after arrival, or placebo. Each participant took their assigned medicine for a total of 14 days. There was no difference between the groups in terms of the incidence of clinical viral respiratory infections. However, these colds' duration was significantly shorter and severity substantially less in the black elder group than the placebo. There was no difference between the two groups' adverse effects, suggesting no significant danger from black elders (Tiralongo et al., 2020). The development of these natural anti-influenza agents for clinical use will further extend the portfolio of drugs for prophylactic treatment of severe flu epidemics or pandemic.

4.6 | Enterovirus 71 and medicinal plants

Enterovirus 71 (EV71) is a pathogenic species of the Picornaviridae family. EV71 comprises a single positive RNA genome with approximately 7.5 kb. It was observed throughout a modest epidemic in California between 1969 and 1972 (Schmidt et al., 1974). EV71 became the most infective enterovirus serotypes, causing several global outbreaks. EV71 inflammation develops rashes, and vesicular lesions on the hands, legs, and oral mucosa. It sometimes develops fatal congenital abnormalities such as aseptic meningitis, encephalitis, acute respiratory disease, and pulmonary edema. A fecal-oral route mainly delivers EV71, but transfer by a respiratory droplet is indeed conceivable. It's among the most prominent reasons for hand-foot and mouth disease (HFMD) in young kids, often associated with severe neurological disorders that can be devastating (Tapparel et al., 2013). The risk of transmission in children below 5 years of age is reasonably high in endemic regions, and several epidemics had already happened during the last few millennia.

Preventive EV71 vaccines were currently developed, and palliative care is being used to improve the symptoms. However, many other natural products and herbal medicines exhibited inhibitory activity against EV71 infection (Table 3). The analysis revealed that *O. basilicum* extracts and isolated compounds effectively prevent EV71 disease and replication (Chiang et al., 2005). In contrast, raoulic acid recognized as a CVB inhibitor suppresses EV71 (Choi et al., 2009). Similarly, epigallocatechin gallate from green tea tamper with EV71 replication by modulating the redox cell environment (H. Y. Ho et al., 2009). Gallic acid from *Woodfordia fruticosa* flowers showed anti-EV71 activity (Choi et al., 2010). Anti-EV71 activity of chrysosplenetin and penduletin, two o-methylated flavonols confined from the leaves of *Laggera pterodonta*, showed vigorous anti-EV71 activity with low cytotoxicity. Throughout the time-of-addition assay, all compounds impeded progeny virus development and RNA replication by almost 100% when incorporated within 4 hr post-infection (Zhu et al., 2011). In relation, there were studies undertaken to study the antiviral capabilities of various plant or algae-derived EV 71-containing compounds (Chiu et al., 2012; Lin et al., 2009; Wang et al., 2011a; Wang et al., 2012d; Wang et al., 2013; Yang et al., 2012).

Contrary, phytochemicals evaluated for EV71 antiviral activity showed low cytotoxicity. Some of them, such as aloe-emodin, (Lin et al., 2008) extract of *H. cordata*, kappa carrageenan (Chiu et al., 2012) extract of *Kalanchoe gracilis*, and extract of *Paris polyphylla* Smith (Wang et al., 2011b) have a precise molecular mechanism(s) of action. The research tries to evaluate 12 frequently used antiviral herbs preferred by Chinese government agencies for the HFMD. *H. cordata* found the only remedy with potent antiviral activity against both EV71. These study results may justify follow-up experiments to determine the precise molecular mechanisms of action and to analyze the plant's anti-EV71 capability in the animal study (Chen et al., 2013). Chebulagic acid, isolated from *Terminalia chebula* fruit, displayed

antiviral activity against human enterovirus 71 in vitro and in vivo models. Its treatment significantly reduced the viral cytopathic effect on rhabdomyosarcoma cells with an IC_{50} of 12.5 μg/ml. The use of chebulagic acid therapy in patients with enterovirus 71 effectively reduced mortality and alleviated clinical symptoms by inhibiting viral replication. Chebulagic acid may be a potent pharmacological entity to influence enterovirus 71 infections (Yang et al., 2013). Hederasaponin B and 30% ethanol extract of *Hedera helix* against EV71 subgenotypes C3 and C4a in Vero cells showed vigorous antiviral activity by lowering visible development CPE. It further impeded viral VP2 protein expression, implying the suppression of viral capsid protein synthesis (Hong et al., 2015; Song et al., 2014). Without appropriate medical care to prevent and treat EV71 infection, further studies are needed to explore novel enteroviral antivirals.

4.7 | Respiratory syncytial virus and medicinal plants

RSV is an enshrouded negative-stranded ssRNA virus belonging to the Paramyxoviridae family. RSV is a prevalent virus responsible for respiratory illness in infants and toddlers (Hall, 1994). Almost all children often get afflicted with RSV well before 2 years (Braciale, 2005). It develops mild symptoms and bronchiolitis or pneumonia in infants and immunocompromised patients (Sigurs et al., 2005). Even though RSV causes the most severe illness in premature children, it continues to haunt living beings throughout their lifespan. Immune response to RSV is usually not sufficient to provide protection, but instead, humans are susceptible to reiterated re-infections (Hall et al., 2009; Henderson et al., 1979), that may be life-threatening for older or immune-compromised patients (Falsey & Walsh, 2000). Presently, RSV immunotherapy is not applicable. The therapies available for diagnosing RSV infections like palivizumab (a monoclonal antibody against RSV fusion protein) and ribavirin (nucleoside analog) are slightly effective. Therefore, it is necessary to develop new antivirals to manage RSV infections, and numerous plant-derived natural products were shown to display anti-RSV activity (Table 3).

Uncinoside A and B, the two isolated chromone glycosides from *Selaginella uncinata*, effectively inhibit RSV inflammation, and biflavonoids, namely genkwanol B, genkwanol C, and stellenranol derived from *Radix Wikstroemiae,* are said to have antiviral activity against RSV (Huang et al., 2010; Ma et al., 2003). Further, flavonous 6-C-monoglycosides from *Lophatherum gracile* leaves reported curtailing RSV infection in the cytopathic impact reduction assay (Wang et al., 2012c). Numerous natural anti-RSV therapies such as the herbal prescription (*Cimicifuga foetida* L., and bioactive compound cimicifuga) relieve respiratory diseases (Wang et al., 2011; Wang, Ho, et al., 2012; Wang, Chen, et al., 2012). Furthermore, chebulagic acid and punicalagin hydrolyzable tannins possess antiviral activity toward RSV infection. The two tannins can explicitly inactivate RSV entities and obstruct viral entry aspects, like binding and fusion. They are inadequate against the transmission of RSV post-infection and could contravene the same event in MV, which is another paramyxovirus (Lin et al., 2013). Certain herbal products will help improve the respiratory tract symptoms induced by RSV, like inflammation of the respiratory system to target the viral infection. Resveratrol is one specific illustration documented to stabilize IFN-γlevels and prevent the trachea's inflammation/hyperresponsiveness throughout RSV infection in mice, implying its suitability to minimize airway symptoms triggered by RSV (Zang et al., 2011). Tangeretin and nobiletin (polymethoxylated flavones) obtained from *Citrus reticulate* (Pericarps) impaired RSV replication intracellularly. Tangeretin significantly suppressed RSV phosphoprotein (P protein) expression through virus-cell fusion inhibition at an early stage and cell fusion inhibition at the end of the replication process (Xu et al., 2014). *Schefflera heptaphylla*-derived dicaffeoylquinic acids also hindered RSV replication (Li et al., 2005b). The ethanol extract of *Lophatherum gracile* suppressed RSV infection and inflammation prompted in a dose-dependent manner (Chen et al., 2019).

4.8 | Rotavirus and medicinal plants

Rotavirus is the common cause of chronic gastroenteritis in infants and young children across the globe. It is a paramount public health concern in low-income countries and massive morbidity and mortality rates in advanced nations (Parashar et al., 2006). The genus of rotavirus consists of nine species (A to I), but the only rotavirus A tends to cause more than 90% of human rotavirus infections (Kirkwood, 2010). The rotavirus's genetic material consists of 11 dsRNA segments that code for six structural and six nonstructural proteins. Structural proteins form the rotavirus particle called VP1, VP2, VP3, VP4, VP6, and VP7 premised on their molecular weight. Besides, nonstructural proteins are only produced during cell infection and are called NSP1, NSP2, NSP3, NSP4, NSP5, and NSP. Rotavirus afflicts intestinal cells and causes gastroenteritis; even so, the disease is not restricted to the gastrointestinal tract, and systemic viral transmission has been extensively illustrated (Ramig, 2007; Rivero-Calle et al., 2016).

While there is no particular antiviral drug for rotavirus, several other preventative actions like environmental hygiene and safe food and water can reduce the risk of rotavirus infection (Brown et al., 2013). The U.S. Food and Drug Administration (FDA) certified two subsequent oral attenuated vaccines as an efficient way to prevent rotavirus pandemics. The RotaTeq (Merck), a pentavalent human-bovine vaccine is comprising four rotavirus strains generated by recombination and Rotarix (GlaxoSmithKline), a monovalent human rotavirus vaccine that included one G1P-specific rotavirus strain (Desai et al., 2012; Gurgel et al., 2011). Hence, alternative safe therapies for rotavirus infections have become the subject of ongoing research (Alfajaro et al., 2014). *Pinus koraiensis*, *Lomatium dissectum*, *Artocarpus integrifolia*, *Myristica fragrans*, *Spongias lutea*, *Tylosema esculentum*, *Byrsonima verbascifolia*, *Myracrodruon urundeuva Allemão*, *Eugenia dysenterica*, *Hymenaea courbaril*, and *Achillea kellalensis* were reported to hinders rotaviral strains (Cecílio et al. 2012; Chingwaru et al. 2011; Gandhi et al., 2016; Goncalves et al., 2005; Taherkhani et al., 2013) (Table 4). The active ingredients have not yet been

TABLE 4 List of the potent extracts and bioactive compounds that inhibit Rotavirus

Plant name/Active compounds	Virus strain assessed	Test dose	Culture/Animal model assessed	Proposed mechanism	References
Pinus koraiensis Zucc. (seed Shell)	Human rotavirus	250 μg/ml	African rhesus monkey kidney (MA-104) epithelial cells	Seed shell interferes with virus adsorption by inhibiting CPE of rotavirus in cell cultures	Mukoyama et al., 1991a
Epigallocatechin gallate and theaflavin digallate (green tea)	Human rotavirus (Wa)	IC_{50} 125 μg/ml to 250 μg/ml	MA-104 cells	Interfered with virus adsorption	Mukoyama et al., 1991b
Lomatium dissectum Nutt.	Bovine rotavirus)	Dilutions ranging from 1×10^{-l} through $1 \times l0^{-7}$ of 0.2 ml of extract	MA-104 cells	Inhibited virus induced CPE	McCutcheon et al., 1995
Theobroma cacao Linn. (husk pigment)	Simian rotavirus (SA-11) strain, human rotavirus strains	1 mg/ml	MA-104 cells	Interfered with rotavirus adsorption to cells, also inhibited rotavirus intracellular replications and lessened the infectious viral titer	Gu et al., 2000
Hesperidin and neohesperidin (*Citrus aurantium* Linn.)	Human rotavirus (Wa)	IC_{50} 0.05 mg/ml, 10 μM/ml and 25 μM/ml	MA-104 cells	Hesperidin and neohesperidin exhibited inhibitory effect on rotavirus infection	Kim et al., 2000
Stevian (*Stevia rebaudiana*)	Human rotavirus strains and SA-11	EC_{50} 431–492 μg/ml	MA-104 cells	Inhibitory activity against the replication of four serotypes of human rotavirus (HRV) and inhibited the binding of VP7 to the infected cells	Takahashi et al., 2001
Stevia rebaudiana Bertoni.	Human rotavirus and SA-11	EC_{50} 32–153 μg/ml	MA-104 cells	Inhibitory activity against the virus replication and binding of viral proteins VP7 not VP4 to the infected cells	Takahashi et al., 2001
Artocarpus integrifolia Linn. *Myristica fragrans* Houtt. and *Spongias lutea* Linn.	SA-11 and Human (HCR3) rotaviruses in MA-104 cells	(480 μg/ml), (160 μg/ml) and (40 μg/ml)	MA-104 cells	Antiviral activity against both the viruses	Goncalves et al., 2005
280 natural compounds	Rotaviruses	IC_{50} 7.5 μg/ml	MA-104 cells	18-β-glycyrrhetinic acid, abietic acid, alltrans-retinoic acid, and mangostin reduced the virus replication as well induced the cell signaling pathways involved in antiviral and inflammatory gene expressions	Shaneyfelt et al., 2006
Vaccinium macrocarpon Aiton, (Juice)	SA-11	1.3, 2.5, 5, 10, 12, 20, 33, and 50% in PBS	MA-104 cells	Inhibited the rotavirus induced hemagglutination reaction and mediated the anti-rotavirus activity	Lipson et al., 2007
Aegle marmelos Linn.	SA-11	0.51 mg/ml ± 0.005 mg/ml, 2.55 mg/ml ± 0.025 mg/ml and 5.11 mg/ ml ± 0.05 mg/ml	MA-104 cells	Significantly decreased therotoviral infectivity or virus inhibition	Brijesh et al., 2009

TABLE 4 (Continued)

Plant name/Active compounds	Virus strain assessed	Test dose	Culture/Animal model assessed	Proposed mechanism	References
Quillaja saponaria Molina.	Rhesus rotavirus	1–1,000 μg/ml	MA-104 cells	Blocked rotavirus attachment and attenuate infection	Roner et al., 2007
Pectic polysaccharides *(Panax ginseng* C.A. Mey*)*	IC_{50} (15 and 10) μg/m	Human rotavirus (Wa)	MA-104 cells	Protecting cell viability from rotavirus-induced infection. It possibly allievated virus proliferation in cells	Baek et al., 2010
Polyphenols (*Glycyrrhiza uralensis* Fisch)	EC_{50} of polyphenols were 18.7–69.5 μM against G5P[7] and 14.7–88.1 μM against G8P[7]	Bovine rotavirus G8P[7] and porcine rotavirus G5P[7]	Fetal rhesus Monkey kidney (TF-104) cells	Licocoumarone, licoflavonol, glyasperin D and 2′-methoxyisoliquiritigenin showed inhibition viral absorption, viral replication, and viral RNA synthesis	Kwon et al., 2010
Tylosema esculentum Burch.	Rotaviruses human (H4)	0.01 to 0.001 mg/ml	MA-104 cells	Showed profound CPE and interfered with viral replication and strengthened the intestinal epithelial barrier function	Chingwaru et al., 2011
Quillaja saponaria	Rhesus rotavirus	0.015 and 0.0125 mg/mouse (p.o.)	Newborn Balb/c mice/MA104 cells	Alleviated rotavirus infection by coating target cells and hence reduce rotavirus induced diarrhea	Tam and Roner, 2011
Vaccinium macrocarpon (juice) and *Vitis labrusca* Linn. (juice)	SA-11	50% concentration of juices in PBS	MA-104 cells	Showed associated loss of RNA integrity of viral capsid protein	Lipson et al., 2011
Psidium guajava Linn.	SA-11	0.027 ± 0.001 mg/ml, 0.027 ± 0.013 mg/ml, 1.350 ± 0.063 mg/ml and 2.7 ± 0.125 mg/ml	MA-104 cells	Decreased the cell death in virus infected cells	Birdi et al., 2011
Nelumbo nucifera Gaertn. *Aspalathus linearis*, *Urtica dioica* Linn. *Glycyrrhiza glabra* Linn. and *Olea europaea* Linn.	SA-11 and the Rhesus rotavirus Strain	IC_{50} < 300 μg/ml	MA-104 cells	Exerted antiviral activities and has no positive effect on the maintenance of trans-epithelial resistance	Knipping et al., 2012
Glycyrrhiza uralensis	Porcine rotavirus K85 (G5P[7]) Strain	100, 200, and 400 mg/ml (p.o.)	Colostrum deprived piglets/TF-104 cells	Cured rotavirus diarrhea and down-regulated proinflammatory cytokines and its related transcription factor and signaling molecules	Alfajaro et al., 2012
Proanthocyanidins (Vaccinium macrocarpon and *Vitis labrusca)*	SA-11	1,000 μg/ml in PBS	MA-104 cells	Proanthocyanidins effectively blocked capsid protein (VP6) binding to host cells	Lipson et al., 2012
Vaccinium macrocarpon and *Vitis labrusca*	SA-11	50% concentrations of juices in PBS	MA-104 cells	Cranberry juice was most effective at pH 2.7 and grape juice at a suspension pH of 6.7.	Cecílio et al., 2012
Alpinia katsumadai	Bovine G8P(7) and porcine G5P(7]) rotaviruses	EC_{50} 0.7 ± 0.4 to 33.7 ± 6.5 μg/ml against G5P(7) strainEC_{50} 8.4 ± 2.2μg/ml, 6.5 ± 0.8μg/ml, and 8.4 ± 5.0 μg/ml against G8P(7) strain	MA-104 cells	Blocked viral adsorption	Kim et al., 2012

(Continues)

TABLE 4 (Continued)

Plant name/Active compounds	Virus strain assessed	Test dose	Culture/Animal model assessed	Proposed mechanism	References
Achillea kellalensis Boiss.	Bovine rotavirus	EC_{50} 100 μg/ml	MA-104 cells	Prevented viral replication and inhibited the viral CPE	Taherkhani et al., 2013
Tannins (*Diospyros kaki* Linn.)	Viral strains	0.05%, 0.025% and 0.005% of tannins	MA-104 cells	Inhibited attachment of the virus to the cells	Ueda et al., 2013
Rice bran (*Oryza sativa* Linn.)	Human rotavirus(VirHRV)Wa strain(G1P1A[8])	10% of the pigs total daily calorie	Neonatal gnotobotic pigs	Rice bran promoted thedevelopment of IFN-T cell responses, total IgM IgSCs in ileum and spleen, total IgA IgSCs in spleen and blood, and total serum IgM, IgA, and IgG antibody production	Yang et al., 2014
Achyrocline bogotensis DC.	Rhesus rotavirus	Substances dissolved in DMSO to a 100 mg/ml; dilutions μg/ml 0–1.000 down	MA-104 cells	Exhibited antirotaviral activity characterized by a virucidal effect and by the reduction of the infectious particles produced post-infection	Taherkhani et al., 2015
Eucalyptus camaldulensis Dehnh. (essential oils)	Human rotavirus (Wa) strain	1/10 dilutions	MA-104 cells	Reduced viral titres against rotavirus	El-Baz et al., 2015
Achillea fragrantissima Linn. *Nitraria retusa* (Forssk.) Asch	Human rotavirus (Wa) strain	IC_{50} 1.0–1.2 mg/ml and IC_{50} 0.9–1.4 mg/ml	MA-104 cells	Reduced viral titres against rotavirus	Mohamed et al., 2015
α-Glucosyl hesperitin and epigallocatechin gallate	SA-11	100×10^3 μg/ml nd 80, 160, and 320 μg/ml	MA-104 cells	Loss of viral capsid protein	Huang et al., 2015
Genistein	Human rotavirus (Wa) and SA-11 strain	>160 μM	MA-104 human epithelial colorectal (Caco2) cells	Genistein inhibited rotavirus replication by upregulating AQP4 expression via the cAMP/PKA/CREB signaling pathway	Lipson et al., 2015
Resveratrol, Piceatannol, Trans-arachidin-1 and Transarachidin-3	SA-11	10–20 μM	Human adenocarcinoma intestinal cell lines (HT29 FT8) and MA-104 cells	Two stilbenoids, trans-arachidin-1 and transarachidin-3 showed therapeutic potential against rotavirus replication via downregulating NSP4 protein levels	Ball et al., 2015
Myracrodruon urundeuva	SA-11	50–500 μg/ml	MA-104 cells	Diminished the multiplication of the virus including inhibiting the CPE	Cecílio et al., 2016

isolated and characterized from the above-described plant species. Further, chemical investigations are needed to explore plant species' chemical compounds in mass quantities and display more inhibitory effects toward rotavirus than that of the extract.

Aegle marmelos, *Quillaja saponaria*, *Psidium guajava*, *Nelumbo nucifera*, *Aspalathus linearis*, *Urtica dioica*, *G. glabra*, *Olea europaea*, *Achyrocline bogotensis*, *Eucalyptus camaldulensis*, *Achillea fragrantissima*, *Nitraria retusa*; *Rindera lanata*, and *Euphorbia hirta* were reported as novel antiviral candidates toward rotavirus infection. They interfere with virus absorption, inhibits virus replication, and reduces the levels of virus titers (Birdi et al., 2011; Brijesh et al., 2009; Civra et al., 2017; El-Baz et al., 2015; Knipping et al., 2012; Mohamed et al., 2015; Pilau et al., 2011; Roner et al., 2010; Téllez, Téllez, Vélez, & Ulloa, 2015). Besides, *Vaccinium macrocarpon*, *Vitis labrusca*, and *Myracrodruon urundeuva* (Cecílio et al., 2016; Lipson et al. 2007, 2011, 2012) decreases the level of external viral capsid proteins and influences the virulence of rotavirus. Similarly, bioactive compounds such as licocoumarone, licoflavonol, glyasperin D and 2′-methoxyisoliquiritigenin, carvacrol, 18β-glycyrrhetinic acid, luteolin, vitexin, apigenin-7-O-glucoside, and tannins from *Diospyros kaki* (Ebenaceae) inhibits the rotavirus infection of MA-104. Similarly, epigallocatechin gallate, theaflavin digallate, genistein, hesperidin, neohesperidin, diosmin, pectic polysaccharides isolated from the *Panax ginseng*; abietic acid, all-trans-retinoic acid, mangostin, α-glucosyl hesperidin, proanthocyanidins from *Vaccinium macrocarpon* and *V. labrusca*; resveratrol, piceatannol, trans-arachidin-1 and trans-arachidin-3, from *Arachis hypogaea* inhibited infections of fetal rhesus monkey kidney (TF-104), human epithelial colorectal (Caco-2), and human adenocarcinoma intestinal (HT29.F8) rotaviruses cultured cells (Baek et al., 2010; Ball et al., 2015; Gandhi et al., 2016; Hardy et al., 2012; H. Huang et al., 2015; Lipson et al., 2012; Pilau et al., 2011; Savi et al., 2010).

The polyphenols like epigallocatechin gallate, 5-007-glucosyl hesperidin, theaflavin, genistein, hesperidin, and neohesperidin, diosmin, luteolin, vitexin, mangostin, licocoumarone, licoflavonol, glyasperin D, and 2′-methoxyisoliquiritigenin were also evaluated for their antiviral activities. Epigallocatechin gallate, ɯglucosyl hesperidin, and genistein are highly water-soluble and significantly increased the virus's structural stability, strongly inhibited rotavirus replication and managed viral protein synthesis (Lipson et al., 2015). Such water-soluble candidates could be appropriate for the growth of novel antiretroviral reactions due to their massive effect on the inhibition of virion protein synthesis. In relation, ursolic acid and resveratrol are noted as a new antiviral molecule that hinders both in vivo and in vitro rotavirus infection (Huang et al., 2020; Tohme et al., 2019).

4.9 | CV and medicinal plants

CV, along with subgroups A (CVA) and B (CVB), is a member of the family Picornaviridae. CV is a non-enveloped positive sensory ssRNA virus frequently transferred by the fecal-oral route and respiratory droplets. The signs of infection would include slight illnesses like fever, malaise, rash, and common colds. However, more severe forms could lead to nervous system diseases, such as aseptic meningitis, encephalitis, and paralysis (Tapparel et al., 2013). CVA is best known as one of the causative agents of HFMD in young children, and CVA group 16 strain (CVA16) is the predominant causative agents of HFMD among CVA (Song et al., 2015).

Unfortunately, hardly any vaccine or effective antibiotic treatments are presently available to avoid CV infections. However, natural ingredients, herbs, and traditional decoctions showed CV-infection therapy (Table 3). A study performed on 76 patients treated with *Sophora* spp. extract reported that RNA clearance of Coxsacki B virus was dose-dependent, and all patients displayed relief from arrhythmia, improved cardiac output, stroke volume, and cardiac index showed progress. The left ventricular mass and its index diminished expressively. The anti-Coxsackie antibody returns to the average titer after 5-months of treatment (Li, 1996).

Aqueous, ethanol extract and bioactive compounds, such as linalool, apigenin, and ursolic acid from *Ocimum basilicum* (sweet basil) reported antiviral activity against CVB1. In particular, Ursolic acid interacts with post-infection replication of CVB1 (Chiang et al., 2005). Further, *Bupleurum kaoi* was known to inhibit CVB1 infection by activating type I interferon response (Cheng et al., 2006b; Cheng et al., 2007). Raoulic acid from *Raoulia australis* was determined as an antiviral informant against many CVB subtypes; however, the mechanism for its influence is uncertain (Choi et al., 2009). *Rheum palmatum* (Polygonaceae) against CV B3 in vitro and in vivo showed inhibitory effects on HEp-2 cells. Extract-treated mice showed improved survival rate, reduced clinical symptoms, and lowered viral titers. The whole study demonstrates that interferon inducers of type I could be useful in maintaining CVB infection and could be further analyzed as a therapeutic intervention (Xiong et al., 2012). Besides, extracts of *Dodonaea viscosa* leaves displayed a therapeutic efficacy ranging from 0.3 to 25 with a reduction in virus titer ranging from 0.25 to 5 log10 TCID 50/0.1 ml against coxackievirus B3 (CVB3) infections. Crude extract provided significant inhibition of CVB3 replication by attaching to the viral capsid of CVB3, and prevents the virus from accessing host cells (Shaheen et al., 2015). *Cornus officinalis*, *Acer triflorum*, *Pulsatilla koreana*, and *Clematis heracleifolia* var. *Davidiana Hemsl* extracts showed significant antiviral activity toward CVA16 (Song et al., 2015). Isatindolignanoside A, a glucosidic indole-lignan isolated from aqueous root extract of *Isatis indigotica* revealed antiviral activity against CVB3 CVB3, with IC_{50} and SI values of 25.9 μM and >3.9, respectively (Meng et al., 2018).

4.10 | Dengue virus and medicinal plants

DENV is an encased positive sensory ssRNA virus of the Flaviviridae family. The DENV is transferred particularly by mosquito bites of *Aedes aegypti* and is an influential arbovirus in Southeast Asia (Black et al., 2002). However, most of the four virus serotypes (DENV 1–4), could trigger dengue fever (Back & Lundkvist, 2013). Clinical symptoms of DENV infection include evident/mild febrile exposure, contemporary dengue fever (fever, headache, myalgia, joint pain, nausea, vomiting, and skin rash), and life-threatening hemorrhage diseases,

explicitly dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) (Sam et al., 2013). Although this is an obsolete viral infection, current vaccination and treatment interventions accessible to prevent and control DENV infection are minimal. The management of dengue-related illnesses entails mosquito-controlled viral infection prevention and the alleviation of infected patients' symptoms.

Developing preventative/pharmacological intervention for DENV infection with natural ingredients could resolve these practical limits. Quite a few natural compounds, like quercetin and narasin, and marine algae derivatives exhibit robust anti-DENV features (Zandi et al., 2011; Low et al., 2011; Koishi et al., 2012) (Table 3). For example, Flavone baicalein shows inhibitory activities against DENV adsorption to host and post-entry viral replication (Zandi et al., 2012). Also, chebulagic acid and punicalagin, extracted from *Terminalia chebula*, have a broad array of antiviral agents against the viruses (Lin et al., 2013). They will effectively inactivate free DENV particles and tamper with attachment and fusion incidents throughout the early viral entry. Nordihydroguaiaretic acid extracted from the leaves of *Larrea tridentata* (Zygophyllaceae) was found to hinder the replication of the linked DENV by approaching genome replication and viral assembly (Soto et al., 2014).

In contrast, flavonoids are the inhibitors of NS2B-NS3 serotype 2 and 3 DENV proteases with IC_{50} values ranging from 15 to 44 μM. Myricetin is non-competitive serotype 2 NS2B-NS3 protease inhibitor with Ki values of 11 and 4.7 μM, respectively (Sousa et al., 2015). Ethanol extracts of *Cassia grandis* leaves, and *Tabernaemontana cymosa* bark toward two DENV serotype 2 strains DENV-2/NG and DENV-2/16681 in VERO, and U937 cells hinders viral replication and significantly impact viral internalization (Hernández-Castroa, Diaz-Castillo, & Martínez-Gutierrez, 2015). The recognition of such natural viral inhibitors may help in building anti-DENV therapy and lower DHF/DSS risk. Schisandrin A extracted from *Schisandra chinensis* hinders DENV replication by up-regulation of antiviral interferon responses through STAT signaling pathway (Yu et al., 2017).

4.11 | MV and medicinal plants

MV is an encased negative-sense ssRNA virus of the Morbillivirus gene (Family: Paramyxoviridae). MV induces measles (an acute respiratory infection characterized by fever, conjunctivitis, coughing, runny nose, and nausea), and a generalized red macular rash across the body resulting in pneumonia encephalitis (Sabella, 2010). Although extremely infectious by interaction with respiratory secretions or airborne particulates, immunotherapies toward measles were described as a three-part MMR vaccine (measles, mumps, and rubella). Despite an effective MV vaccine, the virus remains a vital assassin for children in the developing world (Clements & Cutts, 1995; Murray & Lopez, 1997). A severe further aspect is a resurgence of measles in vaccinated populations and non-immunized individuals (Mossong & Muller, 2003; Zandotti et al., 2004). Such problems highlight MV's medical significance and the need to develop appropriate drug therapies.

Natural products from East and South-east Asian medicinal plants (Kurokawa et al., 1993), the herbal decoction (Huang et al., 1997), the Cherokee remedy spicebush (McWhorter, 1996), plant bioflavonoid isolated from *Rhus succedanea* and *Garcinia multiflora* (Lin et al., 1999), calcium spirulan from the blue-green alga *Spirulina platensis* (Hayashi et al., 1996) and several Rwandan and Ugandan medicinal plant extracts were reported to inhibit MV infection (Cos et al., 2002) (Table 3). In contrast, certain *Olinia rochetiana* (Olkirenyi) and *Warburgia ugandensis* (Osokonoi) typical dietary herbal additives were demonstrated to suppress in vitro MV infection (Parker et al., 2007). Another example is the *Cajanus cajan* extracts recommended to have anti-MV activity, though their bioactive components remain unknown (Nwodo et al., 2011). The chebulagic acid and punicalagin tannins showed potent efficacy against MV infection, mainly by inhibiting the virus particles, disrupting the attachment and fusion stages throughout viral entry (Lin et al., 2013). Therefore, they could serve as potential entry inhibitors to MV.

5 | CONCLUSION AND FUTURE PERSPECTIVES

Antiviral drug production is a concern, as enzymes do not behave like normal living cells and antiviral medications could only deter replication of viruses or inhibit deeper inflammation. Accordingly, plant extracts/botanically derived compounds were documented with potential antiviral activity in cell line and animal model studies. Intriguingly, different mechanisms were established for these compounds, among which virucidal behavior is the most prevalent. Other confirmed exercises include hindering virus entrance into target cells, inhibiting viral protein expressions like 3CLpro, PLpro, S, and ACE2, and interfering with viral DNA replication, all of which are essential prerequisites constructing individual viral particles. Besides, the introduction of high-throughput technologies and traditional medicines together might play a critical role in assessing potential plant-derived substances for innovative discovery in contemporary drug development. They compete against viral diseases but have a long way to go before final use in the clinic to compensate for exploration, isolation, and mechanistic studies. Given the broad diversity of bioactive molecules derived from plants, a reliable, relentless, and constant approach is necessary to pursue unidentified bioactive molecules with potent antiviral activity, particularly relative to the risk posed by pathogenic viruses to enhance resistance to antibiotics. Many natural products like lycorine, homoharringtonine, silvestrol, ouabain, tylophorine glycyrrhetinic acid, acetoxime, and caffeic acid chebulagic acid, punicalagine and 7-methoxycryptopleurine possess significant antiviral activity even in the nanomolar concentration and will be better candidates for novel drug discovery. However, it requires further research to demonstrate the mechanism of secondary metabolites' action in an in vivo and *invitro* model.

In contrast, many natural products with good antiviral activity are the essential components of some traditional food additives that could strengthen the wider public's immune system in inevitable

outbreaks. Further, research must entertain therapeutic agents' feasibility with several other natural sources or with existing drugs, as the multi-target treatment mitigating the chances of drug-resistant viruses being developed. Therefore, comprehensive research in the forthcoming could recognize the possible antiviral molecules and understand their mechanism of action to stabilize such fatal viruses more appropriately.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data are available to share.

ORCID

Venugopalan Venkatesalu https://orcid.org/0000-0002-3753-8432

REFERENCES

Aanouz, I., Belhassan, A., El-Khatabi, K., Lakhlifi, T., El-Ldrissi, M., & Bouachrine, M. (2020). Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. *Journal of Biomolecular Structure & Dynamics*, *6*, 1–9.

Abu-Jafar, A., & Mahmoud, H. (2017). Antiviral activity of *Eucalyptus camaldulensis* leaves ethanolic extract on herpes viruses infection. *International Journal of Clinical Virology*, *1*, 001–009.

Adalja, A., & Inglesby, T. (2019). Broad-spectrum antiviral agents: A crucial pandemic tool. *Expert Review of Anti-infective Therapy*, *17*, 467–470.

Akram, M., Tahir, I. M., Shah, S. M. A., Mahmood, Z., Altaf, A., & Ahmad, K. (2018). Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: A systematic review. *Phytotherapy Research*, *32*, 811–822.

Allahverdiyev, A., Duran, N., Ozguven, M., & Koltas, S. (2004). Antiviral activity of the volatile oils of Melissa officinalis L. against Herpes simplex virus type-2. *Phytomedicine*, *11*(7–8), 657–61. https://doi.org/10.1016/j.phymed.2003.07.01.

Alfajaro, M. M., Kim, H. J., & Park, J. G. (2012). Anti-rotaviral effects of Glycyrrhiza uralensis extract in piglets with rotavirus diarrhea. *Virol J*, *9*, 310. https://doi.org/10.1186/1743-422X-9-310.

Alfajaro, M. M., Rho, M. C., Kim, H. J., Park, J. G., Kim, D. S., Hosmillo, M., … Cho, K. (2014). Anti-rotavirus effects by combination therapy of stevioside and *Sophora flavescens* extract. *Research in Veterinary Science*, *96*, 567–575.

Altemimi, A., Lakhssassi, N., Baharlouei, A., Watson, D. G., & Lightfoot, D. A. (2017). Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. *Plants (Basel)*, *6*, 42.

Alvarez, A. L., Habtemariam, S., Moneim, A. E. A., Melón, S., & Dalton, K. P. (2015). A spiroketal-enol ether derivative from *Tanacetum vulgare* selectively inhibits HSV-1 and HSV-2 glycoprotein accumulation in Vero cells. *Antiviral Research*, *119*, 8–18.

Andersson, S. (2010). General polyhedra, virus structure and mutation. *Zeitschrift für Kristallographie-Crystalline Materials*, *225*, 309–312.

Arduino, P. G., & Porter, S. R. (2008). Herpes Simplex Virus Type 1 infection: overview on relevant clinico-pathological features. *Journal of oral pathology & medicine*, *37*(2), 107–121.

Anggakusuma, Colpitts, C. C., Schang, L. M., Rachmawati, H., Frentzen, A., Pfaender, S., … Steinmann, E. (2013). Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. *Gut*, *63*(7), 1137–1149. https://doi.org/10.1136/gutjnl-2012-304299.

Ansari, J. A., & Inamdar, N. N. (2010). The promise of traditional medicines. *International Journal of Pharmacology*, *6*, 808–812.

Appel, N., Schaller, T., Penin, F., & Bartenschlager, R. (2006). From structure to function: New insights into hepatitis C virus RNA replication. *The Journal of Biological Chemistry*, *281*, 9833–9836.

Appidi, J. R., Grierson, D. S., & Afolayan, A. J. (2008). Ethnobotanical study of plants used for the treatment of diarrhoea in the Eastern Cape, South Africa. *Pakistan Journal of Biological Sciences*, *11*, 1961–1963.

Arunkumar, J., & Rajarajan, S. (2018). Study on antiviral activities, drug-likeness and molecular docking of bioactive compounds of *Punica granatum* L. to Herpes simplex virus - 2 (HSV-2). *Microbial Pathogenesis*, *118*, 301–309.

Atanasov, A. G., Waltenberger, B., Pferschy-Wenzig, E. M., Linder, T., Wawrosch, C., Uhrin, P., … Stuppner, H. (2015). Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnology Advances*, *33*, 1582–1614.

Back, A. T., & Lundkvist, A. (2013). Dengue viruses-an overview. *Infection Ecology & Epidemiology*, *3*, 19839.

Baek, S., Lee, J. G., Park, S. Y., Bae, O. N., Kim, D., & Park, J. H. (2010). Pectic polysaccharides from *Panax ginseng* as the anti-rotavirus principals in Ginseng. *Biomacromolecules*, *11*, 2044–2052.

Ball, J. M., Medina-Bolivar, F., Defrates, K., Hambleton, E., Hurlburt, M. E., Fang, L., … Parr, R. D. (2015). Investigation of stilbenoids as potential therapeutic agents for rotavirus gastroenteritis. *Adv Virol*, *2015*, 293524. https://doi.org/10.1155/2015/293524.

Ball, M. J., Lukiw, W. J., Kammerman, E. M., & Hill, J. M. (2013). Intracerebral propagation of Alzheimer's disease: Strengthening evidence of a herpes simplex virus etiology. *Alzheimer's & Dementia*, *9*, 169–175.

Barquero, A. A., Alche, L. E., & Coto, C. E. (1997). Antiviral activity of meliacine on the replicationof a thymidine kinase-deficient mutant of Herpes simplex virus type 1 alone and in combination with acyclovir. *International Journal of Antimicrobial Agents*, *9*(1), 49–55.

Barbieri, L., Valbonesi, P., & Righi, F. (2000). Polynucleotide: Adenosine glycosidase is the sole activity of ribosome-inactivating proteins on DNA. *Journal of Biochemistry*, *128*, 883–889.

Béjaoui, A., Ben, I., Rokbeni, N., M'rabet, Y., Boussaid, M., & Boulila, A. (2017). Bioactive compounds from *Hypericum humifusum* and *Hypericum perfoliatum*: Inhibition potential of polyphenols with acetylcholinesterase and key enzymes linked to type-2 diabetes. *Pharmaceutical Biology*, *55*, 906–911.

Bekerman, E., & Einav, S. (2015). Infectious disease. Combating emerging viral threats. *Science*, *348*, 282–283.

Ben-Shabat, S., Yarmolinsky, L., Porat, D., & Dahan, A. (2020). Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies. *Drug Delivery and Translational Research*, *10*, 354–367.

Benzekri, R., Bouslama, L., Papetti, A., Hammami, M., Smaoui, A., & Limam, F. (2018). Anti HSV-2 activity of *Peganum harmala* (L.) and isolation of the active compound. *Microbial Pathogenesis*, *114*, 291–298.

Bertol, J. W., Rigotto, C., de Padua, R. M., Kreis, W., Barardi, C. R., & Braga, F. C. (2011). Antiherpes activity of glucoevatromonoside, a cardenolide isolated from a Brazilian cultivar of *Digitalis lanata*. *Antiviral Research*, *92*, 73–80.

Biedenkopf, N., Lange-Grünweller, K., Schulte, F. W., Weiber, A., & Muller, C. (2016). The natural compound silvestrolis a potent inhibitor of Ebola virus replication. *Antiviral Research*, *137*, 76–81.

Birdi, T. J., Daswani, P. G., Brijesh, S., & Tetali, P. (2011). *In vitro* antigiardial and antirotaviral activity of *Psidium guajava* L. leaves. *Indian Journal of Pharmacology*, *43*, 616–617.

Biron, K. K. (2006). Antiviral drugs for cytomegalovirus diseases. *Antiviral Research*, *71*, 154–163.

Black, W. T., Bennett, K. E., Gorrochotegui, E. N., Barillas-Mury, C. V., Fernandez-Salas, I., & Munoz, M. (2002). Flavivirus susceptibility in *Aedes aegypti*. *Archives of Medical Research*, *33*, 379–388.

Bonvicini, F., Lianza, M., Mandrone, M., Poli, F., Gentilomi, G. A., & Antognoni, F. (2018). *Hemidesmus indicus* (L.) R. Br. Extract inhibits the early step of herpes simplex type 1 and type 2 replication. *The New Microbiologica*, *41*, 187–194.

Bosl, K., Ianevski, A., Than, T. T., Andersen, P. I., Kuivanen, S., & Teppor, M. (2019). Common nodes of virus–host interaction revealed through an integrated network analysis. *Frontiers in Immunology*, *4*, 2186.

Braciale, T. J. (2005). Respiratory syncytial virus and T cells: Interplay between the virus and the host adaptive immune system. *Proceedings of the American Thoracic Society*, *2*, 141–146.

Brand, Y. M., Roa-Linares, V. C., Betancur-Galvis, L. A., Durán-García, D. C., & Stashenko, E. (2016). Antiviral activity of *Colombian Labiatae* and Verbenaceae family essential oils and monoterpenes on Human Herpes viruses. *Journal of Essential Oil Research*, *28*, 130–137.

Breitbart, M., & Rohwer, F. (2005). Here a virus, there a virus, everywhere the same virus? *Trends in Microbiology*, *13*, 278–284.

Brezáni, V., Leláková, V., Hassan, S. T. S., Berchová-Bímová, K., Nový, P., & Kloucek, P. (2018). Anti-infectivity against herpes simplex virus and selected microbes and anti-inflammatory activities of compounds isolated from *Eucalyptus globulus* labill. *Viruses*, *10*, 360.

Brijesh, S., Daswani, P., Tetali, P., Antia, N., & Birdi, T. (2009). Studies on the antidiarrhoeal activity of *Aegle marmelos* unripe fruit: Validating its traditional usage. *BMC Complementary and Alternative Medicine*, *9*, 47–59.

Briones, M. S., Dobard, C. W., & Chow, S. A. (2010). Role of human immunodeficiency virus type 1 integrase in uncoating of the viral core. *Journal of Virology*, *84*, 5181–5190.

Brown, J., Cairncross, S., & Ensink, J. H. J. (2013). Water, sanitation, hygiene and enteric infections in children. *Archives of Disease in Childhood*, *98*, 629–634.

Burlone, M. E., & Budkowska, A. (2009). Hepatitis C virus cell entry: Role of lipoproteins and cellular receptors. *The Journal of General Virology*, *90*, 1055–1070.

Burton, D. R., Desrosiers, R. C., Doms, R. W., Koff, W. C., Kwong, P. D., & Moore, J. P. (2004). HIV vaccine design and the neutralizing antibody problem. *Nature Immunology*, *5*, 233–236.

Calland, N., Albecka, A., Belouzard, S., Wychowski, C., Duverlie, G., & Descamps, V. (2012). Epigallocatechin-3-gallate is a new inhibitor of hepatitis C virus entry. *Hepatology*, *55*, 720–729.

Cao, J., Forrest, J. C., & Zhang, X. (2015). A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Research*, *114*, 1–10.

Castillo-Maldonado, I., Moreno-Altamirano, M. M., & Serrano-Gallardo, L. B. (2017). Anti-dengue serotype-2 activity effect of *Sambucus nigra* leaves-and flowers-derived compounds. *Virology: Research & Reviews*, 1–5. https://doi.org/10.15761/VRR.1000117

Cecílio, A. B., Faria, D. B. D., Oliveira, P. D. C., Caldas, S., Oliveira, D. A. D., Sobral, M. E. G., … Almeida, V. L. (2012). Screening of Brazilian medicinal plants for antiviral activity against rotavirus. *Journal of Ethnopharmacology*, *141*, 975–981.

Cecílio, A. B., Oliveira, P. C., Caldas, S., Campana, P. R. V., Francisco, F. L., Duarte, M. G. R., … Almeida, V. L. (2016). Antiviral activity of *Myracrodruon urundeuva* against rotavirus. *Revista Brasileira de Farmacognosia*, *26*, 197–202.

Center for Health Security. (2019). *The characteristics of pandemic pathogens*. Retrieved from http://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2018/180510-pandemic-pathogens-report.pdf

Cesar, G. Z., Alfonso, M. G., Marius, M. M., Elizabeth, E. M., Angel, C. B., & Maira, H. R. (2011). Inhibition of HIV-1 reverse transcriptase, toxicological and chemical profile of *Calophyllum brasiliense* extracts from Chiapas, Mexico. *Fitoterapia*, *82*, 1027–1034.

Chang, J. S., Liu, H. W., Wang, K. C., Chen, M. C., Chiang, L. C., & Hua, Y. C. (2005). Ethanol extract of *Polygonum cuspidatum* inhibits hepatitis B virus in a stable HBV-producing cell line. *Antiviral Research*, *66*, 29–34.

Chang, J. S., Wang, K. C., Liu, H. W., Chen, M. C., Chiang, L. C., & Lin, C. C. (2007). Sho-saiko-to (Xiao-Chai-Hu-Tang) and crude saikosaponins inhibit hepatitis B virus in a stable HBV-producing cell line. *The American Journal of Chinese Medicine*, *35*, 341–351.

Chen, C. J., Michaelis, M., Hsu, H. K., Yang, K. D., Wu, Y. C., Cinatl, J., & Doerr, H. W. (2008). Toona sinensis Roem tender leaf extract inhibits. *Journal of Ethnopharmacology*, *120*, 108–111.

Chen, C. N., Lin, C. P. C., Huang, K. K., Chen, W. C., Hsieh, H. P., Liang, P. H., & Hsu, J. T. A. (2005). Inhibition of SARS-CoV 3C-like protease activity by Theaflavin-3, 3′-digallate (TF3). *Evidence-Based Complementary and Alternative Medicine*, *2*, 209–215.

Chen, F., Yang, L., Huang, Y., Chen, Y., Sang, H., Duan, W., & Yang, J. (2020). Isocorilagin, isolated from *Canarium album* (Lour.) Raeusch, as a potent neuraminidase inhibitor against influenza A virus. *Biochemical and Biophysical Research Communications*, *523*(1), 183–189.

Chen, L. F., Zhong, Y. L., Luo, D., Liu, Z., Tang, W., Cheng, W., … Li, M. M. (2019). Antiviral activity of ethanol extract of Lophatherum gracile against respiratory syncytial virus infection. *Journal of Ethnopharmacology*, *242*, 111575.

Chen, S. G., Leu, Y. L., Cheng, M. L., Ting, S. C., Liu, C. C., Wang, S. D., … Ho, H. Y. (2017). Anti-enterovirus 71 activities of *Melissa officinalis* extract and its biologically active constituent rosmarinic acid. *Scientific Reports*, *7*(1), 12264. https://doi.org/10.1038/s41598-017-12388-2

Chen, X., Wang, C., Xu, L., Chen, X., Wang, W., Yang, G., … Jin, Y. (2013). A laboratory evaluation of medicinal herbs used in china for the treatment of hand, foot, and mouth disease. *Evid Based Complement Alternat Med*, *2013*, 504563. https://doi.org/10.1155/2013/504563.

Chen, X., Wang, Z., Yang, Z., Wang, J., Xu, Y., & Tan, R. (2011). *Houttuynia cordata* blocks HSV infection through inhibition of NF-kB activation. *Antiviral Research*, *92*, 341–345.

Cheng, H. Y., Lin, T. C., Yang, C. M., Wang, K. C., & Lin, C. C. (2004). Mechanism of action of the suppression of herpes simplex virus type 2 replication by pterocarnin A. *Microbes and Infection*, *6*, 738–744.

Cheng, P. W., Ng, L. T., Chiang, L. C., & Lin, C. C. (2006a). Antiviral effects of saikosaponins on human coronavirus 229E in vitro. *Clin Exp Pharmacol Physiol*, *33*, 612–616.

Cheng, P. W., Ng, L. T., Lin, C. C., Xiao, C., & Hu, T. (2006b). Xiao chai hu tang inhibits CVB1 virus infection of CCFS-1 c ells through the induction of Type I interferon expression. *Int Immunopharmacol*, *6*, 1003–12.

Cheng, H. Y., Yang, C. M., Lin, T. C., Shieh, D. E., & Lin, C. C. (2006c). ent-Epiafzelechin-(4alpha-->8)-epiafzelechin extracted from Cassia javanica inhibits herpes simplex virus type 2 replication. *J Med Microbiol*, *55*, 201–206.

Cheng, H. Y., Yang, C. M., Lin, T. C., Lin, L. T., Chiang, L. C., & Lin, C. C. (2011). Excoecarianin, isolated from *Phyllanthus urinaria* Linnea, inhibits herpes simplex virus type 2 infection through inactivation of viral particles. *Evid Based Complement Alternat Med*, *2011*, 259103. https://doi.org/10.1093/ecam/nep157.

Chen, S. D., Gao, H., Zhu, Q. C., Wang, Y. Q., Li, T., & Mu, Z. Q. (2012a). Houttuynoids A-E, anti-herpes simplex virus active flavonoids with novel skeletons from Houttuynia cordata. *Org Lett*, *14*, 1772–1775.

Chen, X., Qiao, H., & Liu, T. (2012b). Inhibition of herpes simplex virus infection by oligomeric stilbenoids through ROS generation. *Antiviral Res*, *95*, 30–36.

Cheng, P. W., Chiang, L. C., Yen, M. H., & Lin, C. C. (2007). *Bupleurum kaoi* inhibits Coxsackie B virus type 1 infection of CCFS-1 cells by induction of type I interferons expression. *Food and Chemical Toxicology*, *45*, 24–23.

Chentoufi, A. A., & Benmohamed, L. (2012). Mucosal herpes immunity and immunopathology to ocular and genital herpes simplex virus infections. *Clin Dev Immunol*, *2012*, 149135. https://doi.org/10.1155/2012/149135.

Chiang, L. C., Ng, L. T., Cheng, P. W., Chiang, W., & Lin, C. C. (2005). Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. *Clinical and Experimental Pharmacology & Physiology*, *32*, 811–816.

Chiang, L. C., Ng, L. T., Liu, L. T., Shieh, D. E., & Lin, C. C. (2003). Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from *Bupleurum* species. *Planta Medica*, *69*, 705–709.

Chingwaru, W., Majinda, R. T., Yeboah, S. O., Jackson, J. C., Kapewangolo, P. T., Kandawa-Schulz, M., & Cencic, A. (2011). *Tylosema esculentum* (Marama) tuber and bean extracts are strong antiviral agents

against rotavirus infection. *Evid Based Complement Alternat Med*, *2011*, 284795. https://doi.org/10.1155/2011/284795.

Chiow, K. H., Phoon, M. C., Putti, T., Tan, B. K., & Chow, V. T. (2016). Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. *Asian Pac J Trop Med*, *9*(1), 1–7. https://doi.org/10.1016/j.apjtm.2015.12.002.

Chiu, Y. H., Chan, Y. L., Tsai, L. W., Li, T. L., & Wu, C. J. (2012). Prevention of human enterovirus 71 infection by kappa carrageenan. *Antiviral Research*, *95*, 128–134.

Cho, J. K., Curtis-Long, M. J., & Lee, K. H.(2013). Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of Paulownia tomentosa [published correction appears in Bioorg Med Chem. *Bioorg Med Chem*, *21*(11), 3051–3057. https://doi.org/10.1016/j.bmc.2013.03.027.

Cho, S. W., Kim, S., Kim, J. M., & Kim, J. S. (2013). Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease. *Nat Biotechnol*, *31*(3), 230–232. https://doi.org/10.1038/nbt.2507.

Cho, Y., & Kim, J. (2017). Effect of Korean red ginseng intake on the survival duration of human immunodeficiency virus type 1 patients. *Journal of Ginseng Research*, *41*, 222–226.

Choi, H. J., Lim, C. H., Song, J. H., Baek, S. H., & Kwon, D. H. (2009). Antiviral activity of raoulic acid from *Raoulia australis* against Picornaviruses. *Phytomedicine*, *16*, 35–39.

Choi, H. J., Song, J. H., Park, K. S., & Baek, S. H. (2010). In vitro anti-enterovirus 71 activity of gallic acid from *Woodfordia fruticosa* flowers. *Letters in Applied Microbiology*, *50*, 438–440.

Choi, J., Jin, Y., Lee, H., Oh, T. W., Yim, N., & Cho, W. (2017). Protective effect of *Panax notoginseng* root water extract against influenza a virus infection by enhancing antiviral interferon-mediated immune responses and natural killer cell activity. *Frontiers in Immunology*, *8*, 1542. https://doi.org/10.3389/fimmu.2017.01542

Choi, J. G., Kim, Y. S., Kim, J. H., & Chung, H. S. (2019). Antiviral activity of ethanol extract of *Geranii Herba* and its components against influenza viruses via neuraminidase inhibition. *Scientific Reports*, *9*, 12132. https://doi.org/10.1038/s41598-019-48430-8

Chuanasa, T., Phromjai, J., Lipipunc, V., Likhitwitayawuid, K., & Suzuki, M. (2008). Anti-herpes simplex virus (HSV-1) activity of oxyresveratrol derived from Thai medicinal plant: Mechanism of action and therapeutic efficacy on cutaneous HSV-1 infection in mice. *Antiviral Research*, *80*, 62–70.

Chung, C. Y., Liu, C. H., Burnouf, T., Wang, G. H., Chang, S. P., Jassey, A., … Lin, L. T. (2016). Activity-based and fraction-guided analysis of *Phyllanthus urinaria* identifies loliolide as a potent inhibitor of hepatitis C virus entry. *Antiviral Research*, *130*, 58–68.

Churqui, M. P., Lind, L., Thörn, K., Svensson, A., Savolainen, O., Aranda, K. T., & Eriksson, K. (2018). Extracts of *Equisetum giganteum* L and *Copaifera reticulate* Ducke show strong antiviral activity against the sexually transmitted pathogen herpes simplex virus type 2. *Journal of Ethnopharmacology*, *210*, 192–197.

Ciesek, S., Von Hahn, T., Colpitts, C. C., Schang, L. M., Friesland, M., & Steinmann, J. (2011). The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. *Hepatology*, *54*, 1947–1955.

Civra, A., Francese, R., & Sinato, D. (2017). *In vitro* screening for antiviral activity of Turkish plants revealing methanolic extract of *Rindera lanata* var. lanata active against human rotavirus. *BMC Complementary and Alternative Medicine*, *17*, 1–8.

Clements, C. J., & Cutts, F. T. (1995). The epidemiology of measles: Thirty years of vaccination. *Current Topics in Microbiology and Immunology*, *191*, 13–33.

Cohen, J. (2020). Wuhan seafood market may not be source of novel virus spreading globally. *Science*, *10*, abb0611.

Cos, P., Hermans, N., De Bruyne, T., Apers, S., Sindambiwe, J. B., & Vanden Berghe, D. (2002). Further evaluation of Rwandan medicinal plant extracts for their antimicrobial and antiviral activities. *Journal of Ethnopharmacology*, *79*, 155–163.

Cos, P., Maes, L., Vlietinck, A., & Pieters, L. (2008). Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection-an update (1998-2007). *Planta Medica*, *74*, 1323–1337.

Cragg, G. M., & Newman, D. J. (2013). Natural products: A continuing source of novel drug leads. *Biochimica et Biophysica Acta*, *1830*, 3670–3695.

Cui, X., Wang, Y., Kokudo, N., Fang, D., & Tang, W. (2010). Traditional Chinese medicine and related active compounds against hepatitis B virus infection. *Bioscience Trends*, *4*, 39–47.

Cyranoski, D. (2020). Mystery deepens over animal source of coronavirus. *Nature*, *579*, 18–19.

Danaher, R. J., Wang, C., Dai, J., Mumper, R. J., & Miller, C. S. (2011). Antiviral effects of blackberry extract against herpes simplex virus type 1. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, *112*, e31–e35.

Dao, T. T., Dang, T. T., Nguyen, P. H., Kim, E., Thuong, P. T., & Oh, W. K. (2012). Xanthones from *Polygala karensium* inhibit neuraminidases from influenza A viruses. *Bioorganic & Medicinal Chemistry Letters*, *22*, 3688–3692.

Dao, T. T., Nguyen, P. H., Lee, H. S., Kim, E., Park, J., & Lim, S. I. (2011). Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from *Glycyrrhiza inflata*. *Bioorganic & Medicinal Chemistry Letters*, *21*, 294–298.

De bing, Y., Neyts, J., & Delang, L. (2015). The future of antivirals: Broad-spectrum inhibitors. *Current Opinion in Infectious Diseases*, *28*, 596–602.

de Clercq, E., & Montgomery, J. A. (1983). Broad-spectrum antiviral activity of the carbocyclic analog of 3-deazaadenosine. *Antiviral Research*, *3*, 17–24.

De Clercq, E. (2000). Current lead natural productsfor the chemotherapy of human immunodeficiency virus (HIV) infection. *Medicinal Research Reviews*, *20*, 323–349.

De Clercq, E., & Li, G. (2016). Approved antiviral drugs over the past 50 years. *Clinical Microbiology Reviews*, *29*, 695–747.

de Sousa, L. R., Wu, H., & Nebo, L. (2015). Flavonoids as noncompetitive inhibitors of Dengue virus NS2B-NS3 protease: inhibition kinetics and docking studies. *Bioorg Med Chem*, *23*(3), https://doi.org/10.1016/j.bmc.2014.12.015.

Desai, R., Curns, A. T., Steiner, C. A., Tate, J. E., Patel, M. M., & Parashar, U. D. (2012). All-cause gastroenteritis and rotavirus-coded hospitalizations among US children, 2000-2009. *Clinical Infectious Diseases*, *55*, e28–e34.

Desselberg, U. (2000). Emerging and re-emerging infectious diseases. *Journal of Infection*, *40*(1), 3–15.

Droebner, K., Ehrhardt, C., Poetter, A., Ludwig, S., & Planz, O. (2007). CYSTUS052, a polyphenol-rich plant extract, exerts anti-influenza virus activity in mice. *Antiviral Research*, *76*(1), 1–10.

Duarte, M. E., Noseda, D. G., Noseda, M. D., Tulio, S., Pujol, C. A., & Damonte, E. B. (2001). Inhibitory effect of sulfated galactans from the marine alga *Bostrychia montagneion* herpes simplex virus replication in vitro. *Phytomedicine*, *8*, 53–58.

Dupre, J., & O'Malley, M. A. (2009). Varieties of living things: Life at the intersection of lineage and metabolism. *Philosophy Theory and Practice in Biology*, *1*, 1–25.

Eccles, R. (2005). Understanding the symptoms of the common cold and influenza. *The Lancet Infectious Diseases*, *5*, 718–725.

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, *4*, 177.

El-Baz, F. K., Mahmoud, K., El-Senousy, W. M., Darwesh, O. M., & ElGohary, A. E. (2015). Antiviral, antimicrobial and schistosomicidal activities of *Eucalyptus camaldulensis* essential oils. *International Journal of Pharmaceutical Sciences Review and Research*, *31*, 262–268.

El-Serag, H. B. (2012). Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*, *142*, 1264–1273.

Fahmy, N. M., Al-Sayed, E., Moghannem, S., Azam, F., El-Shazly, M., & Singab, A. N. (2020). Breaking down the barriers to a natural antiviral agent: Antiviral activity and molecular docking of Erythrina speciosa extract, fractions, and the major compound. *Chemistry & Biodiversity*, *17*, 2. https://doi.org/10.1002/cbdv.201900511

Faith, S. A., Sweet, T. J., Baile, E., Booth, T., & Docherty, J. J. (2006). Resveratrol suppresses nuclear factor-kB in herpes simplex virus infected cells. *Antiviral Research*, *72*, 242–251.

Falsey, A. R., & Walsh, E. E. (2000). Respiratory syncytial virus infection in adults. *Clinical Microbiology Reviews*, *13*, 371–384.

Fatahzadeh, M., & Schwartz, R. A. (2007). Human herpes simplex labialis. *Clinical and Experimental Dermatology*, *32*, 625–630.

Fehr, A. R., Perlman, S., Maier, H. J., Bickerton, E., & Britton, P. (2015). An overview of their replication and pathogenesis; section 2 genomic organization. *Methods in Molecular Biology*, *1282*, 1–23.

Firth, C., Kitchen, A., Shapiro, B., Suchard, M. A., Holmes, E. C., & Rambaut, A. (2010). Using time-structured data to estimate evolutionary rates of double-stranded DNA viruses. *Molecular Biology and Evolution*, *27*, 2038–2051.

Franco, E., Bagnato, B., Marino, M. G., Meleleo, C., Serino, L., & Zaratti, L. (2012). Hepatitis B: Epidemiology and prevention in developing countries. *World Journal of Hepatology*, *4*, 74–80.

Gandhi, G. R., Barreto, P. G., Lima, B. D., Quintans, J. S., Araújo, A. A., Narain, N., … Gurgel, R. Q. (2016). Medicinal plants and natural molecules with *in vitro* and *in vivo* activity against rotavirus: A systematic review. *Phytomedicine*, *23*, 1830–1842.

Gao, W., & Hu, J. (2007). Formation of hepatitis B virus covalently closed circular DNA: Removal of genome-linked protein. *Journal of Virology*, *81*, 6164–6174.

Garozzo, A., Timpanaro, R., Bisignano, B., Furneri, P. M., Bisignano, G., & Castro, A. (2009). In vitro antiviral activity of Melaleuca alternifolia essential oil. *Lett Appl Microbiol*, *49*(6), 806–8. https://doi.org/10.1111/j.1472-765X.2009.02740.x.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burdenof Disease Study 2017. *Lancet*, *392*, 1789–1858.

Geller, C., Varbanov, M., & Duval, R. E. (2012). Human coronaviruses: Insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses*, *4*, 3044–3068.

Geng, Y., Dalhaimer, P., Cai, S., Tsai, R., Tewari, M., Minko, T., & Discher, D. E. (2007). Shape effects of filaments versus spherical particles in flow and drug delivery. *Nature Nanotechnology*, *2*, 249–255.

Geretti, A. M., Armenia, D., & Ceccherini, S. F. (2012). Emerging patterns and implications of HIV-1 integrase inhibitor resistance. *Current Opinion in Infectious Diseases*, *25*, 677–686.

Gescher, K., Kuhn, J., Hafezi, W., Louis, A., Derksen, A., & Deters, A. (2011). Inhibition of viral adsorption and penetration by an aqueous extract from *Rhododendron ferrugineum* L. as antiviral principle against herpes simplex virus type-1. *Fitoterapia*, *82*, 408–413.

Gescher, K., Kuhn, J., Lorentzen, E., Hafezi, W., Derksen, A., & Deters, A. (2011). Proanthocyanidin enriched extract from *Myrothamnus flabellifolia* Welw. exerts antiviral activity against herpes simplex virus type 1 by inhibition of viral adsorption and penetration. *Journal of Ethnopharmacology*, *134*, 468–474.

Ghosh, R. K., Ghosh, S. M., & Chawla, S. (2011). Recent advances in antiretroviral drugs. *Expert Opinion on Pharmacotherapy*, *12*, 31–46.

Goncalves, J. L. S., Lopes, R. C., Oliveira, D. B., Costa, S. S., Miranda, M. M. F. S., Romanosa, M. T. V., … Wigg, M. D. (2005). *In vitro* anti-rotavirus activity of some medicinal plants used in Brazil against diarrhea. *Journal of Ethnopharmacology*, *99*, 403–407.

Gorbalenya, A. E., Enjuanes, L., Ziebuhr, J., & Snijder, E. J. (2006). Nidovirales: Evolving the largest RNA virus genome. *Virus Research*, *117*, 17–37.

Grienke, U., Schmidtke, M., Von, G. S., Kirchmair, J., Liedl, K. R., & Rollinger, J. M. (2012). Influenza neuraminidase: A druggable target for natural products. *Natural Product Reports*, *29*, 11–36.

Guo, C. T., Nakagomi, O., & Mochizuki, M. (1999). Ganglioside GMia on the cell surface is involved in the infection by human rotavirus KUN and MO strains. *The Journal of Biochemistry*, *126*(4), 683–688.

Gurgel, R. Q., Ilozue, C., Correia, J. B., Centenari, C., Oliveira, S. M., & Cuevas, L. E. (2011). Impact of rotavirus vaccination on diarrhea mortality and hospital admissions in Brazil. *Tropical Medicine & International Health*, *16*(9), 1180–1184.

Hafid, A. F., Aoki-Utsubo, C., Permanasari, A. A., Adianti, M., Tumew, L., Widyawaruyanti, A., … Hotta, H. (2017). Antiviral activity of the dichloromethane extracts from *Artocarpus heterophyllus* leaves against hepatitis C virus. *Asian Pacific Journal of Tropical Biomedicine*, *7*, 633–639.

Hafid, A. F., Permanasari, A. A., Tumewu, L., Adianti, M., Aoki, C., Widyawaruyanti, A., … Hotta, H. (2016). Activities of *Ficus fistulosa* leave extract and fractions against Hepatitis C Virus. *Procedia Chemistry*, *18*, 179–184.

Haid, S., Novodomska, A., Gentzsch, J., Grethe, C., Geuenich, S., & Bankwitz, D. (2012). A plant-derived flavonoid inhibits entry of all HCV genotypes into human hepatocytes. *Gastroenterology*, *143*, 213–222.

Hall, C. B. (1994). Prospects for a respiratory syncytial virus vaccine. *Science*, *265*, 1393–1394.

Hall, C. B., Weinberg, G. A., & Iwane, M. K. (2009). The burden of respiratory syncytial virus infection in young children. *N Engl J Med*, *360*(6), 588–598. https://doi.org/10.1056/NEJMoa0804877.

Hao, B. J., Wu, Y. H., Wang, J. G., Hu, S. Q., Keil, D. J., & Hu, H. J. (2012). Hepatoprotective and antiviral properties of isochlorogenic acid A from *Laggera alata* against hepatitis B virus infection. *Journal of Ethnopharmacology*, *144*, 190–194.

Hardy, M. E., Hendricks, J. M., Paulson, J. M., & Faunce, N. R. (2012). 18 β-glycyrrhetinic acid inhibits rotavirus replication in culture. *Virology Journal*, *9*, 96.

Harvey, R. A., Champe, P. C., Fisher, B. D., & Strohl, W. A. (2006). *Lippincott's illustrated reviews: Micobiology* (2nd ed., pp. 354–366). Hagerstown, MD: Lippincott Williams and Wilkins.

Hayashi, T., Hayashi, K., Maeda, M., & Kojima, I. (1996). Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga Spirulina platensis. *Journal of Natural Products*, *59*, 83–87.

He, W., Han, H., Wang, W., & Gao, B. (2011). Anti-influenza virus effect of aqueous extracts from dandelion. *Virology Journal*, *8*, 538.

Helfer, M., Koppensteiner, H., Schneider, M., Rebensburg, S., Forcisi, S., Müller, C., … Brack-Werner, R. (2014). The root extract of the medicinal plant *Pelargonium sidoides* is a potent HIV-1 attachment inhibitor. *PLoS One*, *9*(1), e87487. https://doi.org/10.1371/journal.pone.0087487

Henderson, F. W., Collier, A. M., Clyde, W. A., Jr., & Denny, F. W. (1979). Respiratory syncytial virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *The New England Journal of Medicine*, *300*, 530–534.

Heneidy, S. Z., & Bidak, L. M. (2004). Potential uses of plant species of the coastal mediterranean region, Egypt. *Pakistan Journal of Biological Sciences*, *7*, 1010–1023.

Hernández-Castroa, C., Diaz-Castillo, F., & Martínez-Gutierrez, M. (2015). Ethanol extracts of *Cassia grandis* and *Tabernaemontana cymosa* inhibit the in vitro replication of dengue virus serotype 2. *Asian Pacific Journal of Tropical Disease*, *5*, 98–106.

Ho, G. T., Ahmed, A., Zou, Y. F., Aslaksen, T. H., Wangensteen, G., & Barsett, H. (2015). Structure–activity relationship of immunomodulating pectins from elderberries. *Carbohydrate Polymers*, *125*, 314–322.

Ho, G. T., Zou, Y. F., Aslaksen, T. H., Wangensteen, G., & Barsett, H. (2016). Structural characterization of bioactive pectic polysaccharides

from elderflowers (*Sambuci flos*). *Carbohydrate Polymers*, *135*, 128–137.

Ho, H. Y., Cheng, M. L., Weng, S. F., Leu, Y. L., & Chiu, D. T. (2009). Antiviral effect of epigallocatechin gallate on enterovirus 71. *Journal of Agricultural and Food Chemistry*, *57*, 6140–6147.

Ho, T. Y., Wu, S. L., Chen, J. C., Li, C. C., & Hsiang, C. Y. (2007). Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral research*, *74*(2), 92–101. https://doi.org/10.1016/j.antiviral.2006.04.014.

Hober, D., Sane, F., Jaidane, H., Riedweg, K., Goffard, A., & Desailloud, R. (2012). Immunology in the clinic review series; focus on type 1 diabetes and viruses: Role of antibodies enhancing the infection with Coxsackievirus-B in the pathogenesis of type 1 diabetes. *Clinical and Experimental Immunology*, *168*, 47–51.

Hong, E. H., Song, J. H., Shim, A., Lee, B. R., Kwon, B. E., Song, H. H., … Ko, H. J. (2015). Coadministration of *Hedera helix* L. extract enabled mice to overcome insufficient protection against influenza A/PR/8 virus infection under suboptimal treatment with oseltamivir. *PLoS One*, *10*, e0131089.

Horrix, C., Raviv, Z., Flescher, E., Voss, C., & Berger, M. R. (2011). Plant ribosome-inactivating proteins type II induce the unfolded protein response in human cancer cells. *Cellular and Molecular Life Sciences*, *68*, 1269–1281.

Hsieh, C. F., Chen, Y. L., Lin, C. F., Ho, J. Y., Huang, C. H., Chiu, C. H., … Horng, J. T. (2016). An extract from *Taxodium distichum* targets hemagglutinin- and neuraminidase-related activities of influenza virus in vitro. *Scientific Reports*, *6*, 36015. https://doi.org/10.1038/srep36015

Hu, D. S., Azhar, E. I., Madani, T. A., & Ntoumi, F. (2020). The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. *International Journal of Infectious Diseases*, *91*, 264–266.

Huang, H., Liao, D., Liang, L., Song, L., & Zhao, W. (2015). Genistein inhibits rotavirus replication and upregulates AQP4 expression in rotavirus-infected Caco-2 cells. *Archives of Virology*, *160*, 1421–1433.

Huang, H., Liao, D., Zhou, G., Zhu, Z., Cui, Y., & Pu, R. (2020). Antiviral activities of resveratrol against rotavirus *in vitro* and *in vivo*. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *77*, 153230.

Huang, S. P., Shieh, G. J., Lee, L., Teng, H. J., Kao, S. T., & Lin, J. G. (1997). Inhibition effect of shengma-gegen-tang on measles virus in Vero cells and human peripheral blood mononuclear cells. *The American Journal of Chinese Medicine*, *25*, 89–96.

Huang, T. J., Tsai, Y. C., & Chiang, S. Y. (2014). Anti-viral effect of a compound isolated from *Liriope platyphylla* against hepatitis B virus *in vitro*. *Virus Research*, *192*, 16–24.

Huang, W., Zhang, X., Wang, Y., Ye, W., Ooi, V. E., & Chung, H. Y. (2010). Antiviral biflavonoids from *Radix Wikstroemiae (Liaogewanggen)*. *Chinese Medicine*, *5*, 23.

Huang, T. J., Tsai, Y. C., & Chiang, S. Y. (2014). Anti-viral effect of a compound isolated from Liriope platyphylla against hepatitis B virus in vitro. *Virus Res*, *192*, 16–24. https://doi.org/10.1016/j.virusres.2014.07.015.

Huerta-Reyes, M., Basualdo Mdel, C., Abe, F., Jimenez-Estrada, M., Sole, C., & Reyes-Chilpa, R. (2004). HIV-1 inhibitory compounds from *Calophyllum brasiliense* leaves. *Biological & Pharmaceutical Bulletin*, *27*, 1471–1475.

Hung, P. Y., Ho, B. C., Lee, S. Y., Chang, S. Y., Kao, C. L., & Lee, S. S. (2015). *Houttuynia cordata* targets the beginning stage of herpes simplex virus infection. *PLoS One*, *10*, e0115475.

Husain, A., Kaushik, A., Awasthi, H., Singh, D. P., Khan, R., & Mani, D. (2017). Immunomodulatory and antioxidant activities of fresh juice extracts of Brahmi and Guduchi. *Indian Journal of Traditional Knowledge*, *16*, 498–505.

Ianevski, A., Andersen, P. I., Merits, A., Bjoras, M., & Kainov, D. (2019). Expanding the activity spectrum of antiviral agents. *Drug Discovery Today*, *24*, 1224–1228.

Jang, J. W., Choi, J. Y., & Kim, Y. S (2018). Effects of virologic response to treatment on short-and long-term outcomes of patients with chronic hepatitis B virus infection and decompensated cirrhosis. *Clinical Gastroenterology and Hepatology*, *16*(12), 1954–63.

Jegede, A., Offor, U., Onanuga, I., Naidu, E., & Azu, O. (2017). Effect of co-administration of *Hypoxis hemerocallidea* extract and antiretroviral therapy (HAART) on the histomorphology and seminal parameters in Sprague Dawley rats. *Andrologia*, *49*, 45–50.

Jeong, H. J., Kim, Y. M., Kim, J. H., Kim, J. Y., Park, J. Y., & Park, S. J. (2012). Homoisoflavonoids from *Caesalpinia sappan* displaying viral neuraminidases inhibition. *Biological & Pharmaceutical Bulletin*, *35*, 786–790.

Jiang, Z. Y., Liu, W. F., Zhang, X. M., Luo, J., Ma, Y. B., & Chen, J. J. (2013). Anti-HBV active constituents from *Piper longum*. *Bioorganic & Medicinal Chemistry Letters*, *23*, 2123–2127.

Jung, J., Kim, N. K., & Park, S. (2015). Inhibitory effect of *Phyllanthus urinaria* L. extract on the replication of lamivudine-resistant hepatitis B virus *in vitro*. *BMC Complementary and Alternative Medicine*, *15*, 255.

Kapoor, R., Sharma, B., & Kanwar, S. S. (2017). Antiviral phytochemicals: An overview. *Biochemistry & Physiology*, *6*, 220. https://doi.org/10.4172/2168-9652.1000220

Karimi, A., Mohammadi-Kamalabadi, M., Rafieian-Kopaei, M., & Amjad, L. (2016). Determination of antioxidant activity, phenolic contents and antiviral potential of methanol extract of *Euphorbia spinidens* Bornm (Euphorbiaceae). *Tropical Journal of Pharmaceutical Research*, *15*, 759–764.

Kim, S. K., & Karadeniz, F. (2011). Anti-HIV activity of extracts and compounds from marine algae. *Advances in food and nutrition research*, *64*, 255–65.

Kim, H. H., Kwon, H. J., & Ryu, Y. B. (2012). Antiviral activity of Alpinia katsumadai extracts against rotaviruses. *Res Vet Sci*, *92*(2), 320–3. https://doi.org/10.1016/j.rvsc.2010.11.012.

Kwon, H. J., Kim, H. H., & Ryu, Y. B. (2010). In vitro anti-rotavirus activity of polyphenol compounds isolated from the roots of Glycyrrhiza uralensis. *Bioorganic & medicinal chemistry*, *18*(21), 7668–7774.

Kim, D. E., Min, J. S., Jang, M. S., Lee, J. Y., Shin, Y. S., Park, C. M., & Kwon, S. (2019). Natural bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. *Biomolecules*, *9*, 696.

Kim, K., Kim, K. H., Kim, H. Y., Cho, H. K., Sakamoto, N., & Cheong, J. (2010). Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway. *FEBS Letters*, *584*, 707–712.

Kim, D. W., Seo, K. H., & Curtis-Long, M. J. (2014a). Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. *J Enzyme Inhib Med Chem*, *29*, 59–63.

Kim, O., Yoo, S., & Yoo, D. (2014b). Immunomodulatory effects of Curcuma longa L. extract in LP-BM5 murine leukemia viruses-induced murine acquired immune deficiency syndrome. *J Korean Soc Food Sci Nutr*, *43*, 1317–1324.

Kim, J. H., Kim, K., & Kim, W. (2020). Genipin inhibits rotavirus-induced diarrhea by suppressing viral replication and regulating inflammatory responses. *Sci Rep*, *10*(1), 15836. https://doi.org/10.1038/s41598-020-72968-7.

Kirkwood, C. D. (2010). Genetic and antigenic diversity of human rotaviruses: Potential impact on vaccination programs. *The Journal of Infectious Diseases*, *202*, S43–S48. https://doi.org/10.1086/653548

Knipping, K., Garssen, J., & Land, B. V. (2012). An evaluation of the inhibitory effects against rotavirus infection of edible plant extracts. *Virology Journal*, *9*, 137.

Koffuor, G., Dickson, R., Gbedema, S., Ekuadzi, E., Dapaah, G., & Otoo, L. (2014). The immunostimulatory and antimicrobial property of two herbal decoctions used in the management of HIV/AIDS in Ghana. *African Journal of Traditional, Complementary and Alternative Medicines*, *11*, 166–172.

Koishi, A. C., Zanello, P. R., Bianco, E. M., Bordignon, J., dos, N. D., & Santos, C. (2012). Screening of dengue virus antiviral activity of marine

seaweeds by an *in situ* enzyme linked immunosorbent assay. *PLoS One*, *7*(12), 7, e51089.

Kudo, E., Taura, M., Matsuda, K., Shimamoto, M., Kariya, R., & Goto, H. (2013). Inhibition of HIV-1 replication by a tricyclic coumarin GUT-70 in acutely and chronically infected cells. *Bioorganic & Medicinal Chemistry Letters*, *23*, 606–609.

Kuo, Y. C., Kuo, Y. H., Lin, Y. L., & Tsai, W. J. (2006). Yatein from *Chamaecyparis obtusa* suppresses herpes simplex virustype 1 replication in HeLa cells by interruption the immediate-early gene expression. *Antiviral Research*, *70*, 112–120.

Kuo, Y. C., Lin, L. C., Tsai, W. J., Chou, C. H., & Kung, S. H. (2002). Samarangenin B from *Limonium sinense* suppress herpes simplex virus type1 replication in vero cells by regulation of viral macromolecular synthesis. *Antimicrobial Agents and Chemotherapy*, *46*, 2854–2864.

Kurokawa, M., Ochiai, H., Nagasaka, K., Neki, M., Xu, H., & Kadota, S. (1993). Antiviral traditional medicines against herpes simplex virus (HSV-1), poliovirus, and measles virus *in vitro* and their therapeutic efficacies for HSV-1 infection in mice. *Antiviral Research*, *22*, 175–188.

Kurokawa, M., Nagasaka, K., Hirabayashi, T., Uyama, S., Sato, H., Kageyama T., … Namba, T. (1995). Efficacy of traditional herbal medicines in combination with acyclovir against herpes simplex virus type 1 infection in vitro and in vivo. *Antiviral Research*, *27*, 19–37. https://doi.org/10.1016/0166-3542(94)00076-k

Kwon, H., & Lok, A. S. (2011). Hepatitis B therapy. *Nature Reviews. Gastroenterology & Hepatology*, *8*, 275–284.

Kwon, H. J., Ryu, Y. B., Kim, Y. M., Song, N., Kim, C. Y., Rho, M. C., & Park, S. J. (2013). In vitro antiviral activity of phlorotannins isolated from Ecklonia cava against porcine epidemic diarrhea coronavirus infection and hemagglutination. *Bioorganic & Medicinal Chemistry*, *21*, 4706–4713.

Ky, J. M. K., Zerbo, P., Gnoula, C., Simpore, J., Nikiema, J. B., & Millogo-Rasolodimby, J. (2009). Medicinal plants used in traditional medicine in the centre east region of Burkina Faso. *Pakistan Journal of Biological Sciences*, *12*, 1287–1298.

Lau, K. M., Lee, K. M., Koon, C. M., Cheung, C. S., Lau, C. P., & Ho, H. M. (2008). Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *Journal of Ethnopharmacology*, *118*, 79–85.

Lavoie, S., Côté, I., Pichette, A., Gauthier, C., Ouellet, M., Nagau-Lavoie, F., … Legault, J. (2017). Chemical composition and anti-herpes simplex virus type 1 (HSV-1) activity of extracts from *Cornus canadensis*. *BMC Complementary and Alternative Medicine*, *17*, 123. https://doi.org/10.1186/s12906-017-1618-2

Leyton, L., Hott, M., Acuña, F., Caroca, J., Nuñez, M., Martin, C., … Otth, C. (2015). Nutraceutical activators of AMPK/Sirt1 axis inhibit viral production and protect neurons from neurodegenerative events triggered during HSV-1 infection. *Virus Research*, *205*, 63–72.

Li, B., Guo, Q. L., & Tian, Y. (2016). New anti-HBV C-boivinopyranosyl flavones from *Alternanthera philoxeroides*. *Molecules*, *21*, 336.

Li, D. (1996). Research progress and clinical application of matrine type. *Chinese Traditional and Herbal Drugs*, *27*, 308–310.

Li, S. Y., Chen, C., Zhang, H. Q., Guo, H. Y., Wang, H., & Wang, L. (2005a). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antivir Res*, *67*, 18–23.

Li, F. Y., But, P. P. H., & Ooi, V. E. C. (2005b). Antiviral activity and mode of action of caffeoylquinic acids from Schefflera heptaphylla (L). *Antiviral Res*, *68*, 1–9.

Li, J., Zhou, B., & Li, C. (2015). Lariciresinol-4-O-β-D-glucopyranoside from the root of Isatis indigotica inhibits influenza A virus-induced pro-inflammatory response. *J Ethnopharmacol*, *174*, 379–386. https://doi.org/10.1016/j.jep.2015.08.037.

Li, F. (2016). Structure, function, and evolution of coronavirus spike proteins. *Annual Review of Virology*, *3*, 237–261.

Li, T., Liu, L., Wu, H., Chen, S., Zhu, Q., & Gao, H. (2017). Anti-herpes simplex virus type 1 activity of Houttuynoid A, a flavonoid from *Houttuynia cordata* Thunb. *Antiviral Research*, *144*, 273–280.

Liang, T. J. (2009). Hepatitis B: The virus and disease. *Hepatology*, *49*(5 Suppl), S13–S21.

Lin, C. W., Tsai, F. J., Tsai, C. H., Lai, C. C., Wan, L., & Ho, T. Y. (2005). Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. *Antiviral Research*, *68*, 36–42.

Lin, C. W., Wu, C. F., Hsiao, N. W., Chang, C. Y., Li, S. W., Wan, L., … Lin, W. Y. (2008). Aloe-emodin is an interferon-inducing agent with antiviral activity against Japanese encephalitis virus and enterovirus 71. *International Journal of Antimicrobial Agents*, *32*, 355–359.

Lin, L. T., Chen, T. Y., Chung, C. Y., Noyce, R. S., Grindley, T. B., & McCormick, C. (2011). Hydrolyzable tannins (chebulagic acid and punicalagin) target viral glycoprotein-glycosaminogly can interactions to inhibit herpes simplex virus 1 entry and cell to cell spread. *Journal of Virology*, *85*, 4386–4398.

Lin, L. T., Chen, T. Y., Lin, S. C., Chung, C. Y., Lin, T. C., & Wang, G. H. (2013). Broad-spectrum antiviral activity of chebulagic acid and punicalagin against viruses that use glycosaminoglycans for entry. *BMC Microbiology*, *13*, 187.

Lin, T. Y., Liu, Y. C., Jheng, J. R., Tsai, H. P., Jan, J. T., & Wong, W. R. (2009). Anti-enterovirus 71 activity screening of Chinese herbs with anti-infection and inflammation activities. *The American Journal of Chinese Medicine*, *37*, 143–158.

Lin, Y. M., Flavin, M. T., Schure, R., Chen, F. C., Sidwell, R., & Barnard, D. L. (1999). Antiviral activities of biflavonoids. *Planta Medica*, *65*, 120–125.

Lipson, S. M., Gordon, R. E., Ozen, F. S., Karthikeyan, L., Kirov, N., & Stotzky, G. (2011). Cranberry and grape juices affect tight junctionfunction and structural integrity of rotavirus-infected monkey kidney epithelial cell monolayers. *Food and Environmental Virology*, *3*, 46–54.

Lipson, S. M., Ozen, F. S., Karthikeyan, L., & Gordon, R. E. (2012). Effect of pH on anti-rotavirus activity by comestible juices andproanthocyanidins in a cell-free assay system. *Food and Environmental Virology*, *4*, 168–178.

Lipson, S. M., Ozen, F. S., Louis, S., & Karthikeyan, L. (2015). Comparison of α-glucosyl hesperidin of citrus fruits andepigallocatechingallate of green tea on the loss of rotavirus infectivity in cell culture. *Frontiers in Microbiology*, *6*, 359–369.

Lipson, S. M., Sethi, L., Cohen, P., Gordon, R. E., Tan, I. P., Burdowski, A., & Stotzky, G. (2007). Antiviral effects on bacteriophages and rotavirus by cranberry juice. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *14*, 23–30.

Lipipun, V., Kurokawa, M., & Kurokawa, R. (2003). Efficacy of Thai medicinal plant extracts against herpes simplex virus type 1 infection in vitro and in vivo. *Antiviral Res*, *60*(3), 175–180. https://doi.org/10.1016/s0166-3542(03)00152-9.

Locarnini, S. A., & Yuen, L. (2010). Molecular genesis of drug-resistant and vaccine-escape HBV mutants. *Antiviral Therapy*, *15*, 451–461.

Lovelace, E., Maurice, N., Miller, H., Slichter, C., Harrington, R., & Magaret, A. (2017). Silymarin suppresses basal and stimulus-induced activation, exhaustion, differentiation, and inflammatory markers in primary human immune cells. *PLoS One*, *12*, 171–179.

Low, J. S., Wu, K. X., Chen, K. C., Ng, M. M., & Chu, J. J. (2011). Narasin, a novel antiviral compound that blocks dengue virus protein expression. *Antiviral Therapy*, *16*, 1203–1218.

Lubbe, A., Seibert, I., Klimkait, T., & van der Kooy, F. (2012). Ethnopharmacology in overdrive: The remarkable anti-HIV activity of *Artemisia annua*. *Journal of Ethnopharmacology*, *141*, 854–859.

Ma, F., Shen, W., Zhang, X., Li, M., Wang, Y., & Zou, Y. (2016). AntiHSV activity of Kuwanon X from mulberry leaves with genes expression inhibitory and HSV-1 induced NF-kB deactivated properties. *Biological & Pharmaceutical Bulletin*, *39*, 1667–1674.

Ma, L. Y., Ma, S. C., Wei, F., Lin, R. C., But, P. P., & Lee, S. H. (2003). Uncinoside A and B, two new antiviral chromone glycosides from *Selaginella uncinata*. *Chemical & Pharmaceutical Bulletin*, *51*, 1264–1267.

Ma, S. G., Gao, R. M., Li, Y. H., Jiang, J. D., Gong, N. B., & Li, L. (2013). Antiviral spirooliganones A and B with unprecedented skeletons from the roots of *Illicium oligandrum*. *Organic Letters*, *15*, 4450–4453.

McCutcheon, A. R., Roberts, T. E., & Gibbons, E. (1995). Antiviral screening of British Columbian medicinal plants. *Journal of Ethnopharmacology*, *49*(2), 101–110.

Mahzounieh, M., Moghtadaei, E., & Zahraei Salehi, T. (2006). Detection of calicivirus genome in calves using Ni/E3 primers in Shahrekord area, Iran. *Pakistan Journal of Biological Sciences*, *9*, 227–230.

Makambila-Koubemba, M. C., Mbatchi, B., Ardid, D., Gelot, A., & Henrion, C. (2011). Pharmacological studies of ten medicinal plants used for analgesic purposes in Congo Brazzaville. *International Journal of Pharmacology*, *7*, 608–615.

Marino, Z., Crespo, G., D'Amato, M., Brambilla, N., Giacovelli, G., & Rovati, L. (2013). Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period. *Journal of Hepatology*, *58*, 415–420.

Mathew, D., & Hsu, W. (2018). Antiviral potential of curcumin. *Journal of Functional Foods*, *40*, 692–699.

Meng, L., Guo, Q., & Chen, M. (2018). a glucosidic indole-lignan conjugate from an aqueous extract of the Isatis indigotica roots. *Chinese Chemical Letters*, *29*(8), 1257–1260.

McWhorter, J. H. (1996). Spicebush. A Cherokee remedy for the measles. *North Carolina Medical Journal*, *57*, 306.

Meuleman, P., Albecka, A., Belouzard, S., Vercauteren, K., Verhoye, L., & Wychowski, C. (2011). Griffithsin has antiviral activity against hepatitis C virus. *Antimicrobial Agents and Chemotherapy*, *55*, 5159–5167.

Mohamed, A. A., Ali, S. I., El-Baz, F. K., & El-Senousy, W. M. (2015). New insights into antioxidant and antiviral activities of two wild medicinal plants: *Achillea fragrantissima* and *Nitraria retusa*. *International Journal of Pharma and Bio Sciences*, *6*, 708–722.

Mohammadi, K. M., Karimi, A., Rafieian, M., & Amjad, L. (2014). Phytochemical study and anti viral effect evaluation of methanolic extract with fractions of aerial parts of *Euphorbia spinidens*. *Journal of Babol University of Medical Sciences*, *16*, 25–34.

Monera-Penduka, T., Maponga, C., Wolfe, A., Wiesner, L., Morse, G., & Nhachi, C. (2017). Effect of *Moringa oleifera* Lam. leaf powder on the pharmacokinetics of nevirapine in HIV-infected adults: A one sequence cross-over study. *AIDS Research and Therapy*, *14*, 12. https://doi.org/10.1186/s12981-017-0140-4

Morfin, F., & Thouvenot, D. (2003). Herpes simplex virus resistance to antiviral drugs. *Journal of Clinical Virology*, *26*, 29–37.

Morgan, R. L., Baack, B., Smith, B. D., Yartel, A., Pitasi, M., & Falck-Ytter, Y. (2013). Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. *Annals of Internal Medicine*, *158*, 329–337.

Moss, J. A. (2013). HIV/AIDS review. *Radiologic Technology*, *84*, 247–267.

Mossong, J., & Muller, C. P. (2003). Modelling measles re-emergence as a result of waning of immunity in vaccinated populations. *Vaccine*, *21*, 4597–4603.

Murray, C. J., & Lopez, A. D. (1997). Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*, *349*, 1269–1276.

Mukoyama, A., Ushijima, H., & Nishimura, S. (1991a). Inhibition of rotavirus and enterovirus infections by tea extracts. *Jpn J Med Sci Biol*, *44*(4), 181–6. https://doi.org/10.7883/yoken1952.44.181.

Müller, C., Schulte, F. W., & Lange-Grünweller, K. (2018). Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses.. *Antiviral Res*, *150*, 123–129. https://doi.org/10.1016/j.antiviral.2017.12.010.

Mukoyama, A., Ushijima, H., Unten, S., Nishimura, S., Yoshihara, M., & Sakagami, H. (1991b). Effect of pine seed shell extract on rotavirus and enterovirus infections. *Letters in applied microbiology*, *13*(3), 109–111.

Naik, A., & Juvekar, A. (2003). Effects of alkaloidal extract of *Phyllanthus nirurion* HIV replication. *Indian Journal of Medical Sciences*, *57*, 387–393.

Namazi, R., Zabihollahi, R., Behbahani, M., & Rezaei, A (2013). Inhibitory Activity of Avicennia marina, a Medicinal Plant in Persian Folk Medicine, against HIV and HSV. *Iran J Pharm Res*, *12*(2), 435–443.

Neuman, B. W., Kiss, G., Kunding, A. H., Bhella, D., & Baksh, M. F. (2011). A structural analysis of M protein in coronavirus assembly and morphology. *Journal of Structural Biology*, *174*, 11–22.

Neumann, U. P., Biermer, M., Eurich, D., Neuhaus, P., & Berg, T. (2010). Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy. *Journal of Hepatology*, *52*, 951–952.

Ni, Y. H., & Chen, D. S. (2010). Hepatitis B vaccination in children: The Taiwan experience. *Pathologie et Biologie*, *58*, 296–300.

Nicolas, E., Beggs, J. M., Haltiwanger, B. M., & Taraschi, T. F. (1998). A new class of DNA glycosylase/apurinic/apyrimidinic lyases that act on specific adenines in single stranded DNA. *The Journal of Biological Chemistry*, *273*, 17216–17220.

Nishimura, Y., & Hara, H. (2018). Editorial: Drug repositioning: Current advances and future perspectives. *Frontiers in Pharmacology*, *9*, 1068.

Nocchi, S. R., Companhoni, M. V., de Mello, J. C., Dias Filho, B. P., Nakamura, C. V., Carollo, C. A., … Ueda-Nakamura, T. (2017). Antiviral activity of crude Hydroethanolic extract from *Schinus terebinthifolia* against herpes simplex virus type 1. *Planta Medica*, *83*, 509–518.

Nwodo, U. U., Ngene, A. A., Iroegbu, C. U., Onyedikachi, O. A., Chigor, V. N., & Okoh, A. I. (2011). *In vivo* evaluation of the antiviral activity of *Cajanus cajan* on measles virus. *Archives of Virology*, *156*, 1551–1557.

Okba, M. M., El Gedaily, R. A., & Ashour, R. M. (2017). UPLC–PDA–ESI–qTOF-MS profiling and potent anti-HSV-II activity of *Eucalyptus sideroxylon* leaves. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, *106*, 335–342.

Pacheco, P., Sierra, J., Schmeda-Hirschman, G., Potter, C. W., Jones, B. M., & Moshref, M. (1993). Antiviral activity of chilean medicinal plant extracts. *Phyther. Res*, *7*, 415–418. https://doi.org/10.1002/ptr.2650070606.

Parashar, U. D., Gibson, C. J., Bresee, J. S., & Glass, R. I. (2006). Rotavirus and severe childhood diarrhea. *Emerging Infectious Diseases*, *12*, 304–306.

Paraskevis, D., Kostaki, E. G., Magiorkinis, G., Panayiotakopoulos, G., Sourvinos, G., & Tsiodras, S. (2020). Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infection, Genetics and Evolution*, *79*, 104212.

Park, J. Y., Kim, J. H., Kim, Y. M., Jeong, H. J., Kim, D. W., Park, K. H., & Ryu, Y. B. (2012). Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. *Bioorganic & Medicinal Chemistry*, *20*, 5928–5935.

Park, J. Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., & Lee, W. S. (2017). Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *32*, 504–512.

Parker, M. E., Chabot, S., Ward, B. J., & Johns, T. (2007). Traditional dietary additives of the Maasai are antiviral against the measles virus. *Journal of Ethnopharmacology*, *114*, 146–152.

Partridge, M., & Poswillo, D. E. (1984). Topical carbenoxolone sodium in the management of herpes simplex infection. *The British Journal of Oral & Maxillofacial Surgery*, *22*, 138–145.

Pengsuparp, T., Serit, M., Hughes, S. H., Soejarto, D. D., & Pezzuto, J. M. (1996). Specific inhibition of human immunodeficiency virus type 1 reverse transcriptase mediated by soulattrolide, a coumarin isolated from the latex of *Calophyllum teysmannii*. *Journal of Natural Products*, *59*, 839–842.

Parvez, M. K., Al-Dosari, M. S., Arbab, A. H., Al-Rehaily, A. J., & Abdelwahid, M. A. S. (2020). Bioassay-guided isolation of anti-hepatitis B virus flavonoid myricetin-3-O-rhamnoside along with quercetin from Guiera senegalensis leaves. *Saudi Pharm J*, *28*(5), 550–559. https://doi.org/10.1016/j.jsps.2020.03.006.

Petrera, E., & Coto, C. E. (2009). Therapeutic effect of meliacine, an antiviral derived from *Melia azedarach* L., in mice genital herpetic infection. *Phytotherapy Research*, *23*, 1771–1777.

Pichlmair, A., Schulz, O., Tan, C. P., Naslund, T. I., Liljestrom, P., Weber, F., & Reise, S. C. (2006). RIG-I-mediated antiviral responses to single-stranded RNA bearing 5′-phosphates. *Science*, *314*, 997–1001.

Pilau, M. R., Alves, S. H., Weiblen, R., Arenhart, S., Cueto, A. P., & Lovato, L. T. (2011). Antiviral activity of the *Lippia graveolens* (Mexican oregano) essential oil and its main compound carvacrol against human and animal viruses. *Brazilian Journal of Microbiology*, *42*, 1616–1624.

Piot, P., & Quinn, T. C. (2013). Response to the AIDS pandemic: A global health model. *The New England Journal of Medicine*, *368*, 2210–2218.

Pizzorno, A., Padey, B., Terrier, O., & Rosa-Calatrava, M. (2019). Drug repurposing approaches for the treatment of influenza viral infection: Reviving old drugs to fight against a long-lived enemy. *Frontiers in Immunology*, *10*, 531. https://doi.org/10.3389/fimmu.2019.00531

Pleschka, S. (2013). Overview of influenza viruses. *Current Topics in Microbiology and Immunology*, *370*, 1–20.

Polyak, S. J., Morishima, C., Lohmann, V., Pal, S., Lee, D. Y., & Liu, Y. (2010). Identification of hepatoprotective flavonolignans from silymarin. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 5995–5999.

Polyak, S. J., Morishima, C., Shuhart, M. C., Wang, C. C., Liu, Y., & Lee, D. Y. (2007). Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaB signaling, and HCV infection by standardized Silymarin. *Gastroenterology*, *132*, 1925–1936.

Porter, R. S., & Bode, R. F. (2017). A review of the antiviral properties of Black elder (*Sambucus nigra* L.) products. *Phytotherapy Research*, *31*, 533–554.

Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., & Wells, A. (2019). Drug repurposing: Progress, challenges and recommendations. *Nature Reviews. Drug Discovery*, *18*, 41–58.

Qiu, L. P., & Chen, K. P. (2013). Anti-HBV agents derived from botanical origin. *Fitoterapia*, *84*, 140–157.

Rada, B., & Dragún, M. (1977). Antiviral action and selectivity of 6-azauridine. *Ann NY Acad Sci*, *284*, 410–417. https://doi.org/10.1111/j.1749-6632.1977.tb21977.x.

Rajamohan, F., Kurinov, I. V., Venkatachalam, T. K., & Uckun, F. M. (1999). Deguanylation of human immunodeficiency virus (HIV-1) RNA by recombinant pokeweed antiviral protein. *Biochemical and Biophysical Research Communications*, *263*, 419–424.

Rajtar, B., Skalicka-Woźniak, K., Świątek, Ł., Stec, A., Boguszewska, A., & Polz-Dacewicz, M. (2017). Antiviral effect of compounds derived from *Angelica archangelica* L. on herpes simplex virus-1 and Coxsackievirus B3 infections. *Food and Chemical Toxicology*, *109*, 1026–1031.

Ramig, R. F. (2007). Systemic rotavirus infection. *Expert Review of Anti-infective Therapy*, *5*, 591–612.

Rebensburg, S., Helfer, M., Schneider, M., Koppensteiner, H., Eberle, J., Schindler, M., … Brack-Werner, R. (2016). Potent in vitro antiviral activity of *Cistus incanus* extract against HIV and Filoviruses targets viral envelope proteins. *Scientific Reports*, *6*, 20394. https://doi.org/10.1038/srep20394

Rechtman, M. M., Har-Noy, O., Bar-Yishay, I., Fishman, S., Adamovich, Y., & Shaul, Y. (2010). Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1alpha. *FEBS Letters*, *584*, 2485–2490.

Rehman, S., Ashfaq, U. A., Ijaz, B., & Riazuddin, S. (2018). Anti-hepatitis C virus activity and synergistic effect of *Nymphaea alba* extracts and bioactive constituents in liver infected cells. *Microbial Pathogenesis*, *121*, 198–209.

Reichling, J., Neuner, A., Sharaf, M., Harkenthal, M., & Schnitzler, P. (2009). Antiviral activity of Rhus aromatica (fragrant sumac) extract against two types of herpes simplex viruses in cell culture. *Pharmazie*, *64*(8), 538–541.

Rello, J., & Pop-Vicas, A. (2009). Clinical review: Primary influenza viral pneumonia. *Critical Care*, *13*, 235.

Rittà, M., Marengo, A., Civra, A., Lembo, D., Cagliero, C., Kant, K., … Donalisio, M. (2020). Antiviral activity of a *Arisaema tortuosum* leaf extract and some of its constituents against herpes simplex virus type 2. *Planta Medica*, *86*, 267–275.

Rivero-Calle, I., Gomez-Rial, J., & Martinon-Torres, F. (2016). Systemic features of rotavirus *infection*. *The Journal of Infection*, *72*, S98–S105.

Roh, C. (2012). A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. *Int J Nanomedicine*, *7*, 2173–2179. https://doi.org/10.2147/IJN.S31379.

Roner, M. R., Sprayberry, J., Spinks, M., Dhanji, S. (2007). Antiviral activity obtained from aqueous extracts of the Chilean soapbark tree (Quillaja saponaria Molina). *The Journal of General Virology*, *88*, 275–285. https://doi.org/10.1099/vir.0.82321-0

Roner, M. R., Tam, K. I., & Kiesling-Barrager, M. (2010). Prevention of rotavirus infections in vitro with aqueous extracts of *Quillaja saponaria* Molina. *Future Medicinal Chemistry*, *2*, 1083–1097.

Roschek, B., Jr., Fink, R. C., McMichael, M. D., Li, D., & Alberte, R. S. (2009). Elderberry flavonoids bind to and prevent H1N1 infection *in vitro*. *Phytochemistry*, *70*, 1255–1261.

Rothan, H. A., Zulqarnain, M., Ammar, Y. A., Tan, E. C., Rahman, N. A., & Yusof, R. (2014). Screening of antiviral activities in medicinal plants extracts against denguevirus using dengue NS2B-NS3 protease assay. *Tropical Biomedicine*, *31*, 286–296.

Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J. Y., & Kim, D. (2010). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL^{pro} inhibition. *Bioorganic & Medicinal Chemistry*, *18*, 7940–7947.

Sabella, C. (2010). Measles: Not just a childhood rash. *Cleveland Clinic Journal of Medicine*, *77*, 207–213.

Sagar, S., Kaur, M., & Minneman, K. P. (2010). Antiviral lead compounds from marine sponges. *Marine Drugs*, *8*, 2619–2638.

Sam, S. S., Omar, S. F., Teoh, B. T., Abd-Jamil, J., & AbuBakar, S. (2013). Review of dengue hemorrhagic fever fatal cases seen among adults: A retrospective study. *PLoS Neglected Tropical Diseases*, *7*, e2194.

Samson, M., Pizzorno, A., Abed, Y., & Boivin, G. (2013). Influenza virus resistance to neuraminidase inhibitors. *Antiviral Research*, *98*, 174–185.

Saunders-Hastings, P. R., & Krewski, D. (2016). Reviewing the history of pandemic influenza: Understanding patterns of emergence and transmission. *Pathogens (Basel)*, *5*(4), 66. https://doi.org/10.3390/pathogens5040066

Savi, L. A., Caon, T., Oliveira, A. P. D., Sobottka, A. M., Werner, W., Reginatto, F. H., … Simões, C. M. O. (2010). Evaluation of anti-rotavirus activity of flavonoids. *Fitoterapia*, *81*, 1142–1146.

Schaeffer, D. J., & Krylov, V. S. (2000). Anti-HIV activity of extracts and compounds from algae and cyanobacteria. *Ecotoxicology and Environmental Safety*, *45*, 208–227.

Schmidt, N., Lennette, E. H., & HoAn, H. (1974). Apparently new enterovirus isolated from patients with disease of the central nervous system. *The Journal of Infectious Diseases*, *129*, 304–309.

Schwarz, R. F., Trinh, A., Sipos, B., Brenton, J. D., Goldman, N., & Markowetz, F. (2014). Phylogenetic quantification of intra-tumour heterogeneity. *PLoS Comput Biol*, *10*(4), e1003535. https://doi.org/10.1371/journal.pcbi.1003535.

Soto-Acosta, R., Bautista-Carbajal, P., Syed, G. H., Siddiqui, A., & Del Angel, R. M. (2014). Nordihydroguaiaretic acid (NDGA) inhibits replication and viral morphogenesis of dengue virus. *Antiviral Res*, *109*(132), 40. https://doi.org/10.1016/j.antiviral.2014.07.002.

Schoeman, D., & Fielding, B. C. (2019). Coronavirus envelope protein: Current knowledge. *Virology Journal*, *16*, 69.

Schreiber, C. A., Wan, L., Sun, Y., Lu, L., Krey, L. C., & Lee-Huang, S. (1999). The antiviral agents, MAP30 and GAP31, are not toxic to human spermatozoa and may be useful in preventing the sexual transmission of human immunodeficiency virus type 1. *Fertility and Sterility*, *72*, 686–690.

Shaheen, M., Borsanyiova, M., Mostafa, S., Chawla-Sarkar, M., Bopegamage, S., & El-Esnawy, N. (2015). *In vitro* effect of *Dodonaea viscosa* extracts on the replication of coxackievirus B3 (Nancy) and

rotavirus (SA-11). *Journal of Microbiology and Antimicrobial Agents*, *1*, 47–54.

Shao, W., Li, X., Goraya, M. U., Wang, S., & Chen, J. L. (2017). Evolution of Influenza a virus by mutation and re-assortment. *International Journal of Molecular Sciences*, *18*, 1650.

Shaw, G. M., & Hunter, E. (2012). HIV transmission. *Cold Spring Harbor Perspectives in Medicine*, *2*(11), a006965. https://doi.org/10.1101/cshperspect.a006965

Shaneyfelt, M. E., Burke, A. D., Graff, J. W., Jutila, M. A., & Hardy, M. E. (2006). Natural products that reduce rotavirus infectivity identified by a cell-based moderate-throughput screening assay. *Virol J*, *3*, 68. https://doi.org/10.1186/1743-422X-3-68.

Shen, L., Niu, J., Wang, C., Huang, B., Wang, W., Zhu, N., & Tan, W. (2019). High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. *Journal of Virology*, *93*, e00019.

Shinwari, M. I., & Khan, M. A. (2000). Folk use of medicinal herbs of Margalla Hills National Park, Islamabad. *J Ethnopharmacol*, *69*(1), 45–56. https://doi.org/10.1016/s0378-8741(99)00135-x.

Shoji, M., Woo, S. Y., Masuda, A., Win, N. N., Ngwe, H., Takahashi, E., … Kuzuhara, T. (2017). Anti-influenza virus activity of extracts from the stems of *Jatropha multifida* Linn. collected in Myanmar. *BMC Complementary and Alternative Medicine*, *17*(1), 96. https://doi.org/10.1186/s12906-017-1612-8

Sidwell, R. W., Huffman, J. H., Khare, G. P., Allen, L. B., Witkowski, J. T., & Robins, R. K. (1972). Broadspectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. *Science*, *177*, 705–706.

Sierra, S., Kupfer, B., & Kaiser, R. (2005). Basics of the virology of HIV-1 and its replication. *Journal of Clinical Virology*, *34*, 233–244.

Sigurs, N., Gustafsson, P. M., Bjarnason, R., Lundberg, F., Schmidt, S., & Sigurbergsson, F. (2005). Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *American Journal of Respiratory and Critical Care Medicine*, *171*, 137–141.

Singh, I. P., & Bodiwala, H. S. (2010). Recent advances in anti-HIV natural products. *Natural Product Reports*, *27*, 1781–1800.

Sluis-Cremer, N., & Tachedjian, G. (2008). Mechanisms of inhibition of HIV replication by nonnucleoside reverse transcriptase inhibitors. *Virus Research*, *134*, 147–156.

Song, J., Yeo, S. G., Hong, E. H., Lee, B. R., Kim, J. W., Kim, J., … Ko, H. J. (2014). Antiviral activity of Hederasaponin B from *Hedera helix* against enterovirus 71 subgenotypes C3 and C4a. *Biomolecules and Therapeutics*, *22*, 41–46.

Song, J. H., Park, K., Shim, A., Kwon, B. E., Ahn, J. H., Choi, Y. J., … Ko, H. J. (2015). Complete sequence analysis and antiviral screening of medicinal plants for human coxsackievirus a16 isolated in Korea. *Osong Public Health and Research Perspectives*, *6*, 52–58.

Subashini, M. S., & Rajendran, P. (2015). *In vitro* screening of anti HBV and anti HIV properties of *Gymnema sylvestre* R.Br leaves from Kolli Hills, Tamilnadu, India. *International Journal of Current Microbiology and Applied Sciences*, *4*, 542–547.

Subbarao, K., & Joseph, T. (2007). Scientific barriers to developing vaccines against avian influenza viruses. *Nature Reviews. Immunology*, *7*, 267–278.

Syed, G. H., Amako, Y., & Siddiqui, A. (2010). Hepatitis C virus hijacks host lipid metabolism. *Trends in Endocrinology and Metabolism*, *21*, 33–40.

Taherkhani, R., Farshadpour, F., & Makvandi, M. (2013). *In vitro* anti-rotaviral activity of *Achillea kellalensis*. *Jundishapur Journal of Natural Pharmaceutical Products*, *8*, 138–143.

Takebe, Y., Saucedo, C. J., Lund, G., Uenishi, R., Hase, S., & Tsuchiura, T. (2013). Antiviral lectins from red and blue-green algae show potent *in vitro* and *in vivo* activity against hepatitis C virus. *PLoS One*, *8*, e64449.

Takahashi, K., Matsuda, M., & Ohashi, K. (2001). Analysis of anti-rotavirus activity of extract from Stevia rebaudiana. *Antiviral Research*, *49*(1), 15–24. https://doi.org/10.1016/s0166-3542(00)00134-0.

Tam, K. I., & Roner, M. R. (2011). Characterization of in vivo anti-rotavirus activities of saponin extracts from Quillaja saponaria Molina. *Antiviral Res*, *90*(3), 231–241. https://doi.org/10.1016/j.antiviral.2011.04.0042011.

Tapparel, C., Siegrist, F., Petty, T. J., & Kaiser, L. (2013). Picornavirus and enterovirus diversity with associated human diseases. *Infection, Genetics and Evolution*, *14*, 282–293.

Téllez, M. A., Téllez, A. N., Vélez, F., & Ulloa, J. C. (2015). *In vitro* antiviral activity against rotavirus and astrovirus infection exerted by substances obtained from *Achyrocline bogotensis* (Kunth) DC. (Compositae). *BMC Complementary and Alternative Medicine*, *15*, 428–438.

Theisen, L. L., & Muller, C. P. (2012). EPs (R) 7630 (Umckaloabo (R)), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity *in vitro* and *in vivo*. *Antiviral Research*, *94*, 147–156.

Tiralongo, E., Wee, S. S., & Lea, R. A. (2016). Elderberry Supplementation Reduces Cold Duration and Symptoms in Air-Travellers: A Randomized, Double-Blind Placebo-Controlled Clinical Trial. *Nutrients*, *8*(4), 182. https://doi.org/10.3390/nu8040182.

Thyagarajan, S. P., Thiruneelakantan, K., Subramanian, S., & Sundaravelu, T. (1982). In vitro inactivation of HBsAg by *Eclipta alba* Hassk and *Phyllanthus niruri* Linn. *The Indian Journal of Medical Research*, *76*, 124–130.

Tohmé, M. J., Giménez, M. C., Peralta, A., Colombo, M. I., & Delgui, L. R. (2019). Ursolic acid: A novel antiviral compound inhibiting rotavirus infection in vitro. *Int J Antimicrob Agents*, *54*(5), 601–609. https://doi.org/10.1016/j.ijantimicag.2019.07.015.

Tsai, Y. C., Hohmann, J., El-Shazly, M., Chang, L. K., Dankó, B., Kúsz, N., … Chang, F. R. (2020). Bioactive constituents of *Lindernia crustacea* and its anti-EBV effect via Rta expression inhibition in the viral lytic cycle. *Journal of Ethnopharmacology*, *250*, 112493. https://doi.org/10.1016/j.jep.2019.112493

Ul Qamar, M. T., Alqahtani, S. M., Alamri, M. A., & Chen, L. L. (2020). Structural basis of SARS-CoV-2 $3CL^{pro}$ and anti-COVID-19 drug discovery from medicinal plants. *Journal of Pharmaceutical Analysis*, *10*(4), 313–319.

Ulasli, M., Gurses, S. A., Bayraktar, R., Yumrutas, O., Oztuzcu, S., Igci, M., & Arslan, A. (2014). The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Molecular Biology Reports*, *41*, 1703–1711.

Ueda, K., Kawabata, R., Irie, T., Nakai, Y., Tohya, Y., & Sakaguchi, T. (2013). Inactivation of pathogenic viruses by plant-derived tannins: strong effects of extracts from persimmon (Diospyros kaki) on a broad range of viruses. *PLoS One*, *8*(1), e55343. https://doi.org/10.1371/journal.pone.0055343.

Ulbricht, C., Basch, E., & Cheung, L. (2014). An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the natural standard research collaboration. *Journal of Dietary Supplements*, *11*, 80–120.

Van-der Hoek, L. (2007). Human coronaviruses: What do they cause? *Antiviral Therapy*, *12*, 651–658.

Veiga-Crespo, P., Viñas, M., & Villa, T. (2015). Antiviral compounds of natural origin. In S. Sánchez & A. L. Demain (Eds.), *Antibiotics: current innovations and future trends* (pp. 331–344). Poole: Caister Academic Press. https://doi.org/10.21775/9781908230546.

Venkateswaran, P. S., Millman, I., & Blumberg, B. S. (1987). Effects of an extract from *Phyllanthus nirurion* hepatitis B and woodchuck hepatitis viruses: *in vitro* and *in vivo* studies. *Proceedings of the National Academy of Sciences of the United States of America*, *84*, 274–278.

Venturi, C. R., Danielli, L. J., Klein, F., Apel, M. A., Montanha, J. A., & Bordignon, S. A. L. (2015). Chemical analysis and *in vitro* antiviral and antifungal activities of essential oils from *Glechon spathulata* and *Glechon marifolia*. *Pharmaceutical Biology*, *53*, 682–688.

Vo, T. S., Ngo, D. H., Ta, Q. V., & Kim, S. K. (2011). Marine organisms as a therapeutic source against herpes simplex virus infection. *European Journal of Pharmaceutical Sciences*, *44*, 11–20.

Wang, J., Chen, X., Wan, W., Zhang, Y., Yang, Z., & Jin, Y. (2013). Glycyrrhizic acid as the antiviral component of *Glycyrrhiza uralensis* Fisch. against coxsackievirus A16 and enterovirus 71 of hand foot and mouth disease. *Journal of Ethnopharmacology*, *147*, 114–121.

Wang, M., Cheng, H., Li, Y., Meng, L., Zhao, G., & Mai, K. (1995). Herbs of the genus Phyllanthusin the treatment of chronic hepatitis B: Observations with three preparations from different geographic sites. *The Journal of Laboratory and Clinical Medicine*, *126*, 350–352.

Wang, P., & Tumer, N. E. (1999). Pokeweed antiviral protein cleaves double-stranded supercoiled DNA using the same active site required to depurinate rRNA. *Nucleic Acids Research*, *27*, 1900–1905.

Wang, S. M., Ho, T. S., Lin, H. C., Lei, H. Y., Wang, J. R., & Liu, C. C. (2012). Reemerging of enterovirus 71 in Taiwan: The age impact on disease severity. *European Journal of Clinical Microbiology & Infectious Diseases*, *31*, 1219–1224.

Wang, Y. C., Yi, T. Y., & Lin, K. H. (2011a). In vitro activity of Paris polyphylla smith against enterovirus 71 and Coxsackievirus B3 and its immune modulation. *Am J Chin Med*, *39*, 1219–1234.

Wang, K. C., Chang, J. S., Chiang, L. C., & Lin, C. C. (2011b). Sheng-Ma-Ge-Gen-Tang (Shoma-kakkon-to) inhibited cytopathic effect of human respiratory syncytial virus in cell lines of human respiratory tract. *J Ethnopharmacol*, *135*, 538–544.

Wang, K. S., Chang, J. S., Chiang, L. C., & Lin, C. C. (2012a). Cimicifuga foetida L. inhibited human respiratory syncytial virus in HEp-2 and A549 cell lines. *Am J Chin Med*, *40*, 151–162.

Wang, K. C., Chang, J. S., & Lin, L. T. (2012b). Antiviral effect of cimicifugin from Cimicifuga foetida against human respiratory syncytial virus. *Am J Chin*, *40*, 1033–1045.

Wang, Y., Chen, M., & Zhang, J. (2012c). Flavone C-glycosides from the leaves of Lophatherum gracile and their in vitro antiviral activity. *Planta Med*, *78*, 46–51.

Wang, S. M., Ho, T. S., Lin, H. C., Lei, H. Y., Wang, J. R., & Liu, C. C. (2012d). Reemerging of enterovirus 71 in Taiwan: The age impact on disease severity. *Eur J Clin Microbiol Infect Dis*, *31*, 1219–1224.

Wang, Y., Chen, M., Zhang, J., Zhang, X. L., Huang, X. J., & Wu, X. (2012). Flavone C-glycosides from the leaves of *Lophatherum gracile* and their *in vitro* antiviral activity. *Planta Medica*, *78*, 46–51.

Wang, Y., Wang, X., Xiong, Y., Kaushik, A. C., Muhammad, J., Khan, A., … Wei, D. Q. (2019). New strategy for identifying potential natural HIV-1 non-nucleoside reverse transcriptase inhibitors against drug-resistance: An in silico study. *Journal of Biomolecular Structure & Dynamics*, *38*, 3327–3341.

Wang, T., Xinwei, W., Ya, Z., Changyun, S., Lu, Y., Lijun, M., & Bin, Z. (2020). Antiviral activity of a polysaccharide from *Radix Isatidis* (*Isatis indigotica* Fortune) against hepatitis B virus (HBV) in vitro via activation of JAK/STAT signal pathway. *Journal of Ethnopharmacology*, *257*, 112782. https://doi.org/10.1016/j.jep.2020.112782

Wapling, J., Srivastava, S., Shehu-Xhilaga, M., & Tachedjian, G. (2007). Targeting human immunodeficiency virus type 1 assembly, maturation and budding. *Drug Target Insights*, *2*, 159–182.

Wei, P. H., Wu, S. Z., & Mu, X. M. (2015). Effect of alcohol extract of *Acanthus ilicifolius* L. on anti-duck hepatitis B virus and protection of liver. *Journal of Ethnopharmacology*, *160*, 1–5.

Welsch, C., Jesudian, A., Zeuzem, S., & Jacobson, I. (2012). New direct acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. *Gut*, *61*(Suppl 1), i36–i46.

Wen, C. C., Kuo, Y. H., Jan, J. T., Liang, P. H., Wang, S. Y., Liu, H. G., & Yang, N. S. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *Journal of Medicinal Chemistry*, *50*, 4087–4095.

Wen, C. C., Shyur, L. F., Jan, J. T., Liang, P. H., Kuo, C. J., Arulselvan, P., & Yang, N. S. (2011). Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. *Journal of Traditional and Complementary Medicine*, *1*, 41–50.

WHO. (2013). Retrieved from https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1

WHO. (2015). *WHO publishes list of top emerging diseases likely to cause major epidemics*. Retrieved from https://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/

WHO. (2020). Pneumonia of unknown cause – China, Emergencies preparedness, response. *Disease Outbreak News*. World Health Organization.

Williams-Orlando, C. (2017). Human immunodeficiency virus and herbal medicine. *Alternative and Complementary Therapies*, *23*, 51–59.

Wilson, D., Goggin, K., Williams, K., Gerkovich, M., Gqaleni, N., & Syce, J. (2015). Consumption of *Sutherlandia frutescens* by HIV-seropositive South African adults: An adaptive double-blind randomized placebo controlled trial. *PLoS One*, *10*, 128–132.

Wu, C. Y., Jan, J. T., Ma, S. H., Kuo, C. J., Juan, H. F., Cheng, Y. S. E., & Wong, C. H. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 10012–10017.

Wu, Y. H. (2016). Naturally derived anti-hepatitis B virus agents and their mechanism of action. *World Journal of Gastroenterology*, *22*, 188–204.

Xiong, R., Shen, Y., & Lu, L. (2012). The inhibitory effect of *Rheum palmatum* against coxsackievirus B3 *in vitro* and *in vivo*. *The American Journal of Chinese Medicine*, *40*, 801–812.

Xu, J. J., Wu, X., Li, M. M., Li, G. Q., & Yang, Y. T. (2014). Antiviral activity of polymethoxylated flavones from Guangchenpi, the edible and medicinal pericarps of *Citrus reticulate* 'Chachi'. *Journal of Agricultural and Food Chemistry*, *62*, 2182–2189.

Xu, X. Y., Wang, D. Y, & Ku, C. F. (2019). Anti-HIV lignans from Justicia procumbens. *Chin J Nat Med*, *17*(12), 945–952. https://doi.org/10.1016/S1875-5364(19)30117-7.

Xu, H. Y., Ren, J. H., & Su, Y. (2020). Anti-hepatitis B virus activity of swertisin isolated from Iris tectorum Maxim. *J Ethnopharmacol*, *257*, 112787. https://doi.org/10.1016/j.jep.2020.112787.

Yang, C. M., Cheng, H. Y., Lin, T. C., Chiang, L. C., & Lin, C. C. (2007). Hippomanin A from acetone extract of *Phyllanthus urinaria* inhibited HSV-2 but not HSV-1 infection *in vitro*. *Phytotherapy Research*, *21*, 1182–1186.

Yang, C. W., Lee, Y. Z., Kang, I. J., Barnard, D. L., Jan, J. T., Lin, D., & Lee, S. J. (2010). Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. *Antiviral Research*, *88*, 160–168.

Yang, Y., Zhang, L., Fan, X., Qin, C., & Liu, J. (2012). Antiviral effect of geraniin on human enterovirus 71 in vitro and in vivo. *Bioorganic & Medicinal Chemistry Letters*, *22*, 2209–2211.

Yang, Y., Xiu, J., & Liu, J. (2013). Chebulagic acid, a hydrolyzable tannin, exhibited antiviral activity in vitro and in vivo against human enterovirus 71. *Int J Mol Sci*, *14*(5), 9618–9627. https://doi.org/10.3390/ijms14059618.

Yang, C. W., Lee, Y. Z., & Hsu, H. Y. (2017). Targeting coronaviral replication and cellular JAK2 mediated dominant NF-κB activation for comprehensive and ultimate inhibition of coronaviral activity. *Sci Rep*, *7*(1), 4105. https://doi.org/10.1038/s41598-017-04203-9.

Yang, J, Zheng, Y, & Gou, X (2020). Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*, *94*, 91–95. https://doi.org/10.1016/j.ijid.2020.03.017.

Yao, X., Li, Z., Gong, X., Fu, X., Xiao, X., He, M., … Xu, Z. (2020). Total saponins extracted from Abrus cantoniensis Hance suppress hepatitis B virus replication in vitro and in rAAV8-1.3HBV transfected mice. *Journal of Ethnopharmacology*, *249*, 112366.

Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., & Chen, L. (2004). Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *Journal of Virology*, *78*, 11334–11339.

Yousaf, T., Rafique, S., Wahid, F., Rehman, S., Nazir, A., Rafique, J., … Shah, S. M. (2018). Phytochemical profiling and antiviral activity of

Ajuga bracteosa, *Ajuga parviflora*, *Berberis lycium* and *Citrus lemon* against Hepatitis C Virus. *Microbial Pathogenesis*, *118*, 154–158.

Yu, M. S., Lee, J., Lee, J. M., Kim, Y., Chin, Y. W., & Jee, J. G. (2012). Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. *Bioorganic & Medicinal Chemistry Letters*, *22*, 4049–4054.

Yu, J. S., Wu, Y. H., & Tseng, C. K. (2017). A inhibits dengue viral replication via upregulating antiviral interferon responses through STAT signaling pathway. *Sci Rep*, *7*, 45171. https://doi.org/10.1038/srep45171.

Zakay-Rones, Z., Thom, E., Wollan, T., & Wadstein, J. (2004). Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *The Journal of International Medical Research*, *32*, 132–140.

Zakay-Rones, Z., Varsano, N., & Zlotnik, M. (1995). Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L) during an outbreak of influenza B Panama. *Journal of Alternative and Complementary Medicine*, *1*, 361–369.

Zambon, M. C. (2001). The pathogenesis of influenza in humans. *Reviews in Medical Virology*, *11*, 227–241.

Zandi, K., Teoh, B. T., Sam, S. S., Wong, P. F., Mustafa, M. R., & Abubakar, S. (2011). Antiviral activity of four types of bioflavonoid against dengue virus type-2. *Virology Journal*, *8*, 560.

Zandi, K., Teoh, B. T., Sam, S. S., Wong, P. F., Mustafa, M. R., & Abubakar, S. (2012). Novel antiviral activity of baicalein against dengue virus. *BMC Complementary and Alternative Medicine*, *12*, 214.

Zandotti, C., Jeantet, D., Lambert, F., Waku-Kouomou, D., Wild, F., & Freymuth, F. (2004). Re-emergence of measles among young adults in Marseilles, France. *European Journal of Epidemiology*, *19*, 891–893.

Zang, N., Xie, X., Deng, Y., Wu, S., Wang, L., & Peng, C. (2011). Resveratrol-mediated gamma interferon reduction prevents airway inflammation and airway hyper responsiveness in respiratory syncytial virus-infected immunocompromised mice. *Journal of Virology*, *85*, 13061–13068.

Zeng, F. L., Xiang, Y. F., Liang, Z. R., Wang, X., Huang, D. E., & Zhu, S. N. (2013). Anti-hepatitis B virus effects of dehydrocheilanthifoline from *Corydalis saxicola*. *The American Journal of Chinese Medicine*, *41*, 119–130.

Zhan, P., Jiang, X., & Liu, X. (2010). Naturally occurring and synthetic bioactive molecules as novel non-nucleoside HBV inhibitors. *Mini Reviews in Medicinal Chemistry*, *10*, 162–171.

Zhang, L., Wang, G., Hou, W., Li, P., Dulin, A., & Bonkovsky, H. L. (2010). Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: An analytical review. *Hepatology*, *51*, 690–698.

Zhang, H. J., Rumschlag-Booms, E., & Guan, Y. F. (2017a). Potent Inhibitor of Drug-Resistant HIV-1 Strains Identified from the Medicinal Plant Justicia gendarussa. *J Nat Prod*, *80*(6), 1798–1807. https://doi.org/10.1021/acs.jnatprod.7b00004.

Zhang, H. J., Rumschlag-Booms, E., & Guan, Y. F. (2017b). Anti-HIV diphyllin glycosides from Justicia gendarussa. *Phytochemistry*, *136*, 94–100. https://doi.org/10.1016/j.phytochem.2017.01.005.

Zheng, W., Sun, W., & Simeonov, A. (2018). Drug repurposing screens and synergistic drugcombinations for infectious diseases. *British Journal of Pharmacology*, *175*, 181–191.

Zheng, Y. T., Ben, K. L., & Jin, S. W. (2000). Anti-HIV-1 activity of trichobitacin, a novel ribosome inactivating protein. *Acta Pharmacologica Sinica*, *21*, 179–182.

Zhang, S. Y., Jouanguy, E, & Ugolini, S. (2007). TLR3 deficiency in patients with herpes simplex encephalitis. *Science*, *317*, 1522–1527.

Zhou, B., Yang, Z., Feng, Q., Liang, X., Li, J., Zanin, M., … Zhong, N. (2017). Aurantiamide acetate from *Baphicacanthus cusia* root exhibits anti-inflammatory and anti-viral effects via inhibition of the NF-κB signaling pathway in Influenza A virus-infected cells. *Journal of Ethnopharmacology*, *6*, 60–67.

Zhou, X., Liu, J., Yang, B., Lin, X., Yang, X. W., & Liu, Y. (2013). Marine natural products with anti-HIV activities in the last decade. *Current Medicinal Chemistry*, *20*, 953–973.

Zhu, Q. C., Wang, Y., Liu, Y. P., Zhang, R. Q., Li, X., Su, W. H., … Peng, T. (2011). Inhibition of enterovirus 71 replication by chrysosplenetin and penduletin. *European Journal of Pharmaceutical Sciences*, *44*, 392–398.

Zhuang, M., Jiang, H., Suzuki, Y., Li, X., Xiao, P., Tanaka, T., & Qin, C. (2009). Procyanidins and butanol extract of cinnamomi cortex inhibit SARS-CoV infection. *Antiviral Research*, *82*, 73–81.

How to cite this article: Ali SI, Sheikh WM, Rather MA, Venkatesalu V, Muzamil Bashir S, Nabi SU. Medicinal plants: Treasure for antiviral drug discovery. *Phytotherapy Research*. 2021;1–37. https://doi.org/10.1002/ptr.7039